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EPIVASCULAR CHOROIDAL PIGMENT STREAKS, THEIR PATHOLOGY AND POSSIBLE PROGNOSTIC SIGNIFICANCE

ROY O. SCHOLZ, M.D.

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INTRODUCTION

The epivascular choroidal pigment streaks of albuminuric choroiditis which Siegrist (1) first described have been reported in detail several times in the European literature but are mentioned only a few times in the British and American literature (2). Five patients with this disorder have been observed and in one of these patients a complete autopsy, including the eyes, was studied. A survey of the reported cases revealed the possibility that the appearance of this fundus picture was of general medical and prognostic value. Accordingly, this review was prepared to stimulate further observations of similar patients.

CASE REPORTS

Case 1. D. H. a 42 year old white man was well until August 1940 when he had his first attack of dyspnea while on National Guard manuevers. He was told that he had hypertension and was treated for five months, during which time he remained active as a mechanic but experienced increasing dyspnea with accompanying ankle edema and severe headaches. He was digitalized but his symptoms increased and in January 1941 he reported to the University of Maryland Hospital where his blood pressure measured 280/170. His non-protein-nitrogen was 37 milligrams per cent. Roentgen ray examination showed generalized cardiac enlargement and mild congestive changes. Electrocardiographic studies indicated probable left heart preponderance and probable additional myocardial injury. He was treated for nine months in the out-patient department with potassium thiocyanate with little improvement.

In February, 1941 the patient awoke one morning and found that his right eye was blind. His doctor told him that he had had a hemorrhage. This gradually absorbed. In June of the same year he spilled sulfuric acid into his right eye and was admitted to the Wilmer Institute of the Johns Hopkins Hospital with the diagnosis of kerato-iritis and dermatitis secondary to a chemical burn. The eye examination at that time revealed vision in the right eye to be 20/40 due to the keratitis and mild iritis. Krückenberg spindles were present in both corneas.

Generalized retinal arterial constriction with increased light reflex, arteriovenous compression was present, and punctate hemorrhages were observed near the discs in both eyes. No exudates or pigment deposits were observed. The recovery from the kerato-iritis was prompt and the patient was discharged in a week.

One month later he was admitted to the Baltimore City Hospitals because of cardiac decompensation.

The physical examination at this time was negative except for the cardovascular and ocular systems.

Heart: The apex impulses were diffuse and lay outside the midclavicular line in the fifth interspace. The rate was 100, sounds clear and loud. There was an inconstant gallop rhythm over the base and sternum. Along the sternal border there was a third sound which was apparently a reduplication of the second sound. No murmurs or thrills were found. Peripheral vessels were not remarkable. The blood pressure was 240/140. The abdomen was slightly distended. There was some periumbilical and right upper quadrant tenderness. Liver dullness extended one finger breadth below the costal margin but the liver edge could not be felt.

Eye examination: Retinoscopy and static (5% Homatropine)

$$\text{Right eye: } +50 + 37 \times 180 = 20/20$$

$$\text{Left eye: } +37 + 50 \times 180 = 20/20$$

External examination: Tension and visual fields were all normal.

Slit lamp: Krückenberg Spindles in each cornea.

Ophthalmoscopic: Right eye, Fig. 1. The media were clear and the fundus well seen. The disc was of good color and showed a mild papilloedema on the superior temporal border. The retinal arteries were markedly constricted and the light reflex was moderately increased. There was beading of the inferior temporal artery adjacent to the disc. There was moderate tortuosity of the veins with an increase in the angle of crossing and moderate arterio-venous compression. No hemorrhages or exudates were found in the retina. The whole fundus had a tigroid appearance. In some places the choroidal vessels could not be seen and formed a broad white band (see illustration). About four disc diameters from the disc along sclerosed, but not occluded, choroidal vessels were clumps of black pigment which appeared to cover the vessel. These clumps were directly over the vessel and extended along the vessel, giving the appearance of black beads.

As shown in the illustration, although the largest group of pigmented streaks was found in the superior fundus, they were present in all quadrants.

Left eye: The media were likewise clear and the disc, macula, and vascular tree of the retina were as described in the right eye. The pigment clumps were present over the partially sclerosed choroidal vessels but were finer and less numerous than those observed in the right eye. They were again observed in all quadrants.

Laboratory studies: Urine: 4 + albumin, specific gravity 1.003. Blood counts were normal. Blood chemistry was normal except for a non-protein-nitrogen of 86 on admission and a uric acid of 4.2 milligrams per cent. The patient's general

FIG. 1. EPIVASCULAR CHOROIDAL PIGMENT STRIPES OF ALBUMINURIC CHOROIDITIS, CASE 1., D. H., 42 WM

condition fluctuated considerably. His blood pressure remained almost constant at about 240/140 while his non-protein-nitrogen was between 43 and 86 milligrams per cent. He would become stuporous, seemingly headed for an exitus and recover suddenly. On three occasions he signed the release book only to return to the hospital in acute cardiac decompensation a few days later. During the nine months of observation additional pigment clumps appeared in the choroid adjacent to the previous ones. A few small flame-shaped hemorrhages and small exudates appeared at various times and gradually absorbed. Although mild papilloedema was present, it was never marked. He died in acute decompensation nine months after the pigmented streaks were first observed, and nineteen months after the onset of his hypertensive symptoms.

The medical diagnosis was: 1. Hypertensive cardio-vascular disease, cardiac enlargement and insufficiency, 2. Malignant nephrosclerosis, 3. Hypertensive retinitis, epivascular choroidal pigment streaks, 4. Terminal urinary tract infection. No autopsy was obtained.

Case 2. C. S. a 48 year old white man was well until six weeks before his first admission to The Baltimore City Hospitals. At that time he suddenly began to have attacks of shortness of breath either after rest or shortly after going to bed. These attacks occurred nightly and were accompanied by exertional dyspnea and a feeling of tightness in his chest. His blood pressure was 210/140 and the fundi revealed marked variation of calibre of the arteries. One small retinal hemorrhage was seen. On admission to the hospital the following positive findings were recorded:

Physical examination: The patient's heart was enlarged and his blood pressure was 250/160. The heart sounds were distinct and there was gallop rhythm. There was questionable pleural effusion. Moist râles were heard in both cases.

Eye examination: The patient easily read Jaeger I. External examination, tension and confrontation fields were all normal.

Ophthalmoscopic: Right eye: The media were clear and the fundus well seen. The disc was of good color and showed a normal physiologic cup. Above the disc the margin was slightly blurred but there was no oedema. Immediately below the disc there was a large fluffy exudate. There were noted advanced arteriosclerosis, marked arteriovenous compression and some fullness of the veins. The most remarkable part of the ophthalmoscopic picture was the marked choroidal sclerosis. Some choroidal vessels presented a white cord appearance. In numerous areas in the periphery, particularly at eight o'clock, there were fine speckled deposits of pigment over the choroidal vessels. Left eye: The media were likewise clear and the fundus easily seen. The disc was of good color, cupping and outline. The retinal and choroidal vessels were as described in the right eye. The pigment deposits were similarly distributed over partially sclerosed choroidal vessels. They were not as numerous or heavy in this eye. The largest was seen over a vessel at about five o'clock, starting about two disc diameters from the disc and coursing for about an equal distance.

Laboratory studies: The white blood count was 20,100. Non-protein-nitrogen 46 milligrams per cent. Chlorides 86.2 milliequivalents per liter. Carbon dioxide combining power 70.2 volumes percent. Electrocardiagram was suggestive of acute myocardical infarction of the anterior type.

Course: The patient grew progressively worse. He finally went into a deep coma and died six months after the first discovery of the pigment streaks, and eight months after the onset of his hypertensive symptoms. The medical diagnosis was: 1. Hypertensive cardio-vascular renal disease, cardiac enlargement, 2. Congestive heart failure and pulmonary oedema, chronic passive congestion of the liver, 3. Marked retinal arteriosclerosis, retinal hemorrhages and exudates, 4. Choroidal arteriosclerosis with epivascular choidal pigment streaks. No autopsy was obtained.

Case 3. E. R. a 58 year old white woman who had three episodes of chorea between the ages of 8 and 18 without cardiac sequellae. In 1925 she was found to have syphillis. She was treated in the Johns Hopkins Hospital for gumma of the lungs and clavicle with complete disappearance of both lesions. She had worn glasses since 1926 when she was examined in the Wilmer Institute. At that time she was retinoscoped and found to have marked anisometropia. Right eye: S + 0.25 = 20/20, left eye: S − 7.50 = 20/200. Further examination showed a large myopic crescent and contracted visual field in the left eye. In 1933 another refraction showed right eye: C 0.25 × 45 = 20/15, left eye: S − 6.50 = 4/200.

She was not heard from again until 1942 when she was readmitted to the hospital with a history of incontinence of urine and feces for five weeks, left exophthalmos and lid paralysis for three weeks, and vomiting and severe pain in the left side of her head for two weeks.

Physical examination: The positive findings were: obesity, enlarged heart with a rough systolic murmur over the entire precordium, and a blood pressure of 230/130. There was a profuse vaginal discharge and marked oedema of both feet and legs. Reflexes were sluggish and there was an equivocal Babinski sign on the right.

Eye examination: Vision in the right eye was 20/30-3. In the left eye there was no light preception. Externally the right eye was normal. Corneal sensation was normal in both eyes. There was complete internal and external ophthalmoplegia on the left side with no consensual reaction to light. The left eye was proptosed five millimeters and the patient complained of pain when the globe was compressed. There was no pulsation or bruit.

Opthalmoscopic: Right eye: The media were clear and the disc normal. The arteries showed increased light reflexes. There was marked compression of the arteriovenous crossings. No pigment deposits were seen. Left eye: The media were likewise clear. There was extensive myopic degeneration in the posterior part of the eye. The choroidal vessels were easily seen. About two disc diameters below the disc there was a choroidal vessel dotted with evenly spaced pigment

masses. The streak of pigment dots extended about two disc diameters. The choroidal vessel over which the pigment was deposited was distinctly visible and narrowed but not occluded.

Visual fields: Cooperation was poor and there seemed to be a superior temporal quadrantic defect in the right eye.

Laboratory studies: Blood counts were normal. The urine was normal except for 3 plus albumin. Non-protein-nitrogen was 46 milligrams percent. Albumin was 2.75 grams percent. Albumin-globulin ratio was 43/57. Carbon dioxide combining power was 40.4 volumes percent. A serological test for syphillis was negative. Roentgen ray examination of the head revealed a massive erosion in the neighborhood of the sella turcica.

A diagnosis of pituitary tumor was made. Because of her cardiovascular status it was felt advisable to postpone operative procedures. She was given digitalis and instructed to return when her cardiac status improved.

Three years later an inquiry by letter received the report from her physician that she was under his care for hypertension. Her gait was staggering. Blood pressure was 208/160 millimeters of mercury. The exophthalmos was still present but described as slight and vision in the right eye was normal. In the left eye she counted fingers at 20 centimeters. The probable cause of her neurological disturbance which was previously diagnosed as a pituitary tumor now seemed to have been an intracranial aneurysm.

Case 4. J. H. a 60 year old white male steel worker who was admitted to the Baltimore City Hospitals in a coma which had followed convulsions. There was no reliable informant and the patient later gave only a few relevant details. He had lost the sight of his right eye at the age of 19 following a gunpowder explosion. Otherwise he had been relatively healthy until two years prior to admission when he began treatment for hypertension. He continued to work until the day of admission when he suddenly had a convulsion which was followed by a deep coma.

Physical examination: The positive physical findings were as follows: the patient was in a deep coma; the blood pressure measured 192/110; his heart was enlarged to the left but was otherwise normal. The patient's reflexes were hyperactive; and there was a questionable bilateral positive Babinski. The right eye had a traumatic cataract and posterior synechiae. The left eye was normal externally. The media were clear and disc normal. The arteries were found to be somewhat tortuous and showed increased light streaking. There was marked arterio-venous compression. No hemorrhage or exudate was seen.

Laboratory studies: Blood studies showed a white blood cell count of 11,550 and non-protein-nitrogen of 46. The urine showed a trace of albumin. Roentgen ray examination of the chest later demonstrated moderate cardiac enlargement.

Subsequent course: The patient slowly improved and in three days he was transferred to the chronic ward. He remained relatively comfortable for eleven months at which time he developed severe contact dermatitis. He was readmitted to the medical service and a repeated fundus examination revealed choroidal pigment streaks.

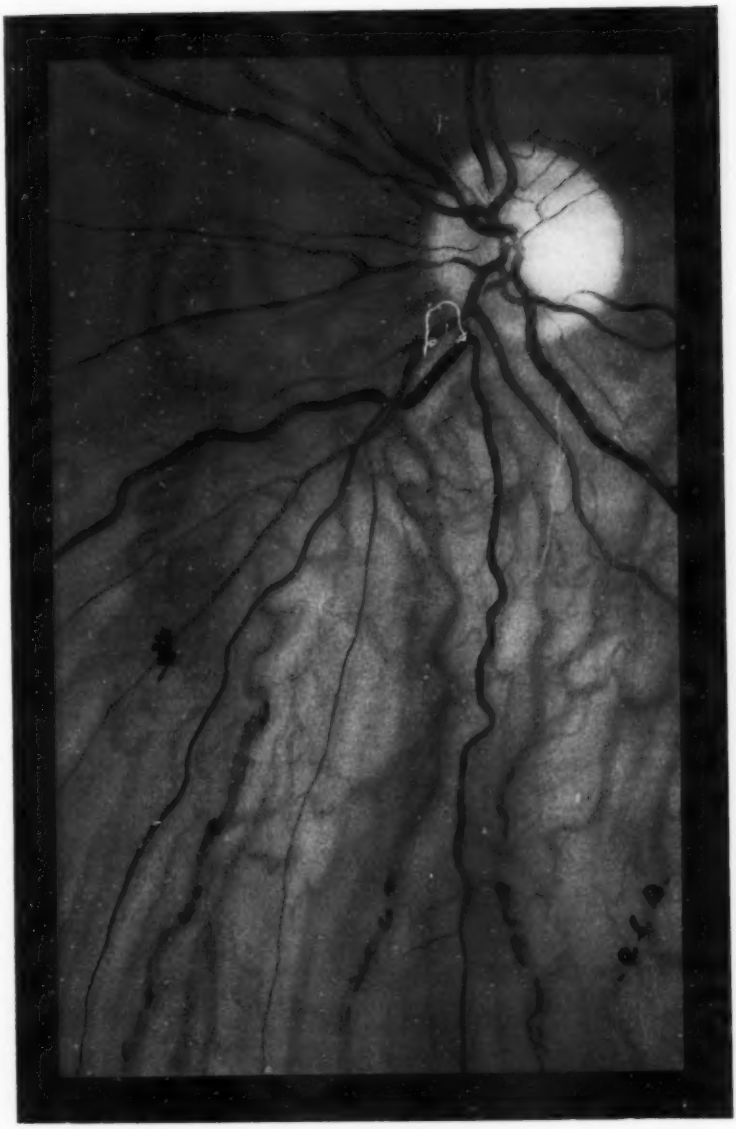

FIG. 2. EPIVASCULAR CHOROIDAL PIGMENT STRIPES OF ALBUMIN CHOROIDITIS, CASE 4, J. H., 61 WM

Eye examination at this time showed no change in the right eye. The traumatic cataract prevented viewing of the fundus. The left eye showed (Fig. 2) clear media and a normal disc. The arteries were narrowed, as before, and there was marked arteriovenous compression. The choroid appeared normal except in the lower half where it was lighter in color. The choroidal vessels were easily visible. About two disc diameters from the disc small accumulations of pigment were arranged along patent choroidal vessels. In the far periphery there were two areas in which the choroidal vessels were seen at white cords. There was no pigment in these areas.

Although the dermatitis cleared the patient steadily went downhill. About eighteen months later he suddenly went into coma and died in two days. Exitus was four and one-half years after the onset of his hypertension and one and one-half years after the fundus picture was discovered.

Medical diagnosis: (1) Hypertensive cardiovascular disease with cardiac enlargement; (2) cerebral thrombosis (old) with pseudobulbar palsy and hemiparesis; (3) recent intracranial hemorrhage.

An autopsy of the viscera was obtained. The anatomical diagnosis was: (1) arteriosclerosis of coronary arteries; (2) terminal lobular pneumonia; (3) acute bronchitis; (4) acute splenic tumor; (5) chronic passive congestion of liver; (6) advanced cerebral arterio-sclerosis; (7) encephalo malacia.

Case 5. R. McC. a 70 year old white man was admitted to the Baltimore City Hospitals for the first time 50 days before his death. His family said he had been ill for two years. His doctor had said he had hardening of the arteries. He was so acutely ill that he could give no history.

Physical examination: Examination was difficult and vision could not be determined. Externally the eyes were normal except for early senile lenticular changes. Tension was normal to fingers.

Ophthalmoscopic: Both eyes: The media were clear except for a slight lenticular haze. The discs were of good color and outline. The maculae were normal and no exudates or hemorrhages were seen. The arteries showed markedly incresaed light reflexes and variations of calibre. Moderate arteriovenous compression was observed. The fundus was tigroid in appearance. About three disc diameters below the right disc there was a string of pigment deposits over a patent choroidal vessel. The vessel was clearly visible and was accompanied by a light colored band on either side in the region of the pigment deposits. Elsewhere there were white cords, wider than an individual choroidal vessel but without pigment deposits. The deposits extended along the vessel several disc diameters into the periphery. In the periphery of the fundus there were occasional spots of pigment over the choroidal vessels. In the left eye only a few scattered dots were seen over the choroidal vessels. No hemorrhages or exudates were seen.

Laboratory studies: Non-protein-nitrogen was 31 milligrams per cent.

Course: The patient gradually became comatose and died 50 days after admission. This was approximately two years after the onset of his hypertension and fifty days after the diagnosis of the epivascular choroidal pigment stripes.

The medical diagnosis was: (1) arteriosclerotic cardiovascular disease, (2) hypertension, (3) cerebral arterial arteriosclerosis and senile degeneration, (4) epivascular choroidal pigment streaking, (5) terminal broncho-pneumonia. A complete autopsy was obtained.[1]

Pathological studies: Gross description: the body was that of an elderly emaciated white male measuring 167 cm. in length. There was no edema. Numerous small angiomota were present on the chest. There were decubitous ulcers on the sacrum, over the trochanters, and on the skin covering the lateral malleoli of the right leg. Several of the teeth were missing. The abdominal and thoracic cavities did not contain any excessive fluid, masses or adhesions.

The heart was slightly enlarged weighing 400 gms. The valves were grossly normal but the aortic valve measured 8 cm. The coronary vessels were sclerotic, especially the anterior descending branch of the left coronary artery. The myocardium showed some diffuse scarring.

The lower lobe of the left lung showed areas of lobular pneumonia while the upper portion was congested. The lower lobe of the right lung was also congested.

The gallbladder was small and contracted, containing two pigment stones about 8 mm. in diameter.

The kidneys weighed 120 gms. each and were in their normal location. They were small and capsules were stripped with some difficulty. The cortex showed areas of scar tissue, narrowing, and numerous discreet small urinary cysts. The medulla was not remarkable. The renal arteries were sclerotic. The bladder contained numerous small yellow stones.

The peripheral vascular systems showed evidence of sclerosis. The aorta contained numerous atheromatous plaques.

The surface of the brain was not remarkable, but a cut section showed numerous areas of softening and cyst formation in the basal ganglia and thalamic regions.

The salient features of the microscopic pathology of the organs were: Prostate fibro adenomatous hyperplasia; liver: chronic passive congestion; testes: decreased spermatogenic activity; pancreas: focal areas of fibrosis, some thickening of the media, and intimal proliferation of the medium sized arteries; heart: increase of intestitial fibrous tissues, hyaline degeneration and extensive fibrous tissue replacement of the myocardium; lungs: aspiration (lipoid) pneumonia, lobular pneumonia; spleen: chronic passive congestion; kidney: arteriolar nephrosclerosis.

The pathological diagnosis was: (1) hypertrophy and dilatation of the left ventricle, (2) generalized arterio sclerosis, (3) encephalomalacia, (4) coronary sclerosis, myocardial infarcts, (5) arteriolar nephrosclerosis, (6) terminal aspiration pneumonia, (7) chronic passive congestion of the lungs and liver, (8) chronic cholecystitis and cholelithiasis, calculi in bladder, (9) choroidal arteriolarsclerosis, patchy occlusion of the choroidal capillaries, proliferation of choroidal pigment epithelium.

Eye pathological studies: The material consisted of the posterior segments

[1] The gross description and the microscopic notes were supplied by Dr. Samuel Pinus of the Baltimore City Hospitals.

of the eyes and optic nerves removed several hours after death and fixed in Bouin's fluid.

Gross examination: Right eye: A study of the material with hand magnification and oblique illumination showed nothing of interest in the position of the streaks. When examined with a slit lamp the retina revealed nothing abnormal, but when this was laid back fine flecks of pigment were seen in a linear arrangement below the disc. They corresponded to the picture seen with the ophthalmoscope before death. The specimen was marked, blocked in paraffine and serial sections 7

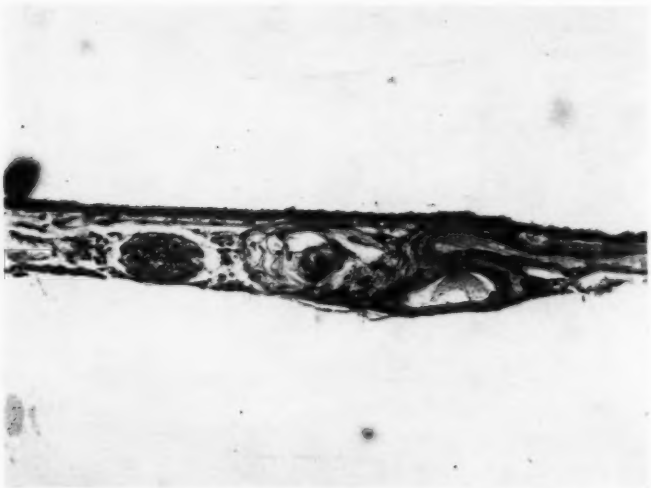

FIG. 3. RIGHT EYE, CASE 5. HEMATOXYLIN AND EOSIN (× 125) CHOROID SHOWING MILD CELL INFILTRATION AND COMPLETELY OCCLUDED CHOROIDAL ARTERIES

microns thick were made. Every fifth section was stained with Voerhoeff-van Gieson's stain the remainder being stained with hematoxylin and eosin. The streaks were not seen grossly in the left eye and this specimen was not sectioned.

Microscopic studies: Right eye: The optic nerve, retina and sclera were normal. The choroid was mildly infiltrated with round cells (Fig. 3) but not more so than usually seen in patients who have a terminal bronchopneumonia. In the same illustration an occluded choroidal vessel is seen. No pigment accumulation were found over this or any of the other occluded choroidal vessels.

At the location of the pigment specks described grossly, an accumulation of proliferated pigment epithelium was found over a choroidal artery (Fig. 4). The individual pigment cells were normal in appearance and rested on a normal Bruch's

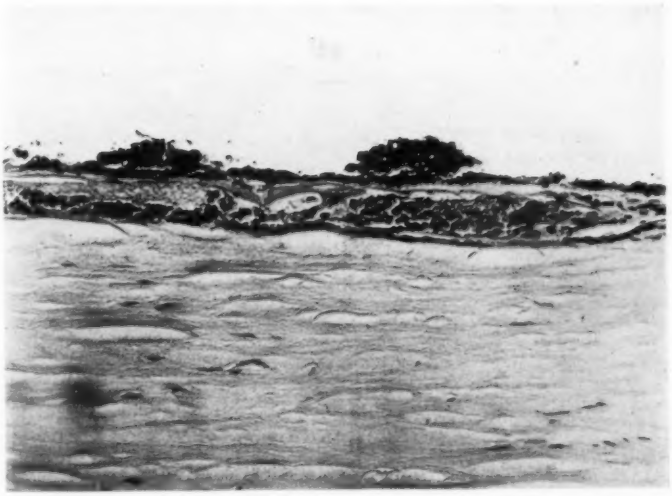

FIG. 4. RIGHT EYE, CASE 5. HEMATOXYLIN AND EOSIN (× 125) PROLIFERATION OF PIGMENT EPITHELIUM OVER PATENT CHOROIDAL ARTERY

FIG. 5. RIGHT EYE, CASE 5. HEMATOXYLIN AND EOSIN (× 750) PROLIFERATION NORMAL APPEARING PIGMENT CELLS
Note absence of choriocapillaris

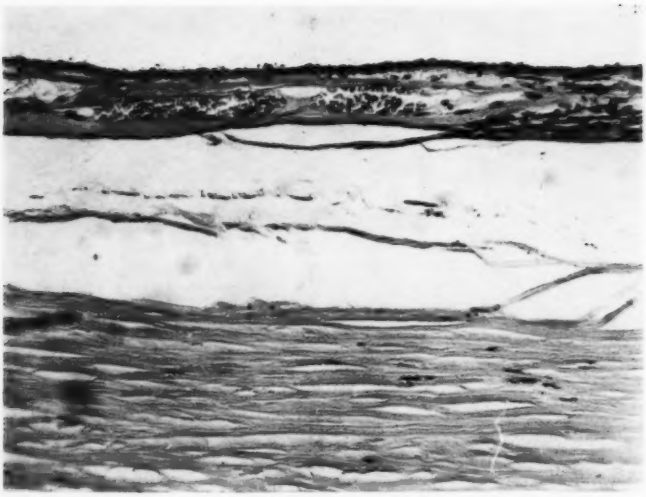

FIG. 6. RIGHT EYE, CASE 5. HEMATOXYLIN AND EOSIN (× 125) THE SAME ARTERY ILLUSTRATED IN FIGURES 4, AND 5, WITH HYALINIZED WALLS

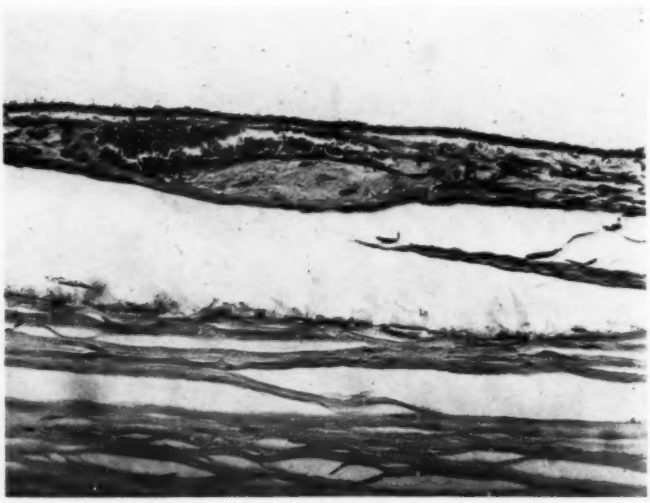

FIG. 7. RIGHT EYE, CASE 5. HEMATOXYLIN AND EOSIN (× 125) THE SAME ARTERY ILLUSTRATED IN FIGURES 4, 5, AND 6

Large hyalinized sclerotic plaque almost occludes lumen

membrane. The chorio-capillaris could not be seen or was occluded over the vessel and in the vicinity of it, (Fig. 5) but was normal in the vicinity of most other vessels. This vessel which was an artery was patent throughout its observed course. Its walls were hyalinized (Fig. 6), and in some areas the lumen was almost occluded by large sclerotic plaques (Fig. 7). The plaque was partially hyalinized and contained some connective tissue cells.

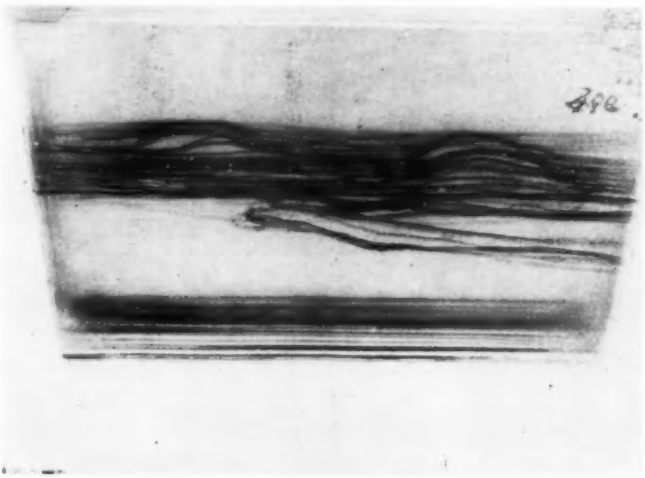

FIG. 8. PHOTOGRAPH OF 3 DIMENSIONAL DIAGRAMMATIC RECONSTRUCTION OF PROLIFERATION OF CHOROIDAL PIGMENT OVER THE PATENT CHOROIDAL BLOOD VESSELS

Magnification factor about 300

Camera lucida drawings of the proliferated pigment epithelium and the vessels they covered were made on cellophane and these diagramatic sketches were piled with glass separators of proportional thickness so as to reconstruct the serial sections magnified 300 times (Fig. 8). This anatomical reconstruction agreed perfectly with the ophthalmoscopic observation and demonstrated the size of the proliferation and their relation to the underlying blood vessels.

REVIEW OF LITERATURE

Clinical studies: Epivascular choroidal pigment deposits were first described clinically and pathologically by Siegrist (1) in 1898. Since then they have been reported on 8 occasions (Table I). In three of these reports the streaks were erroneously classified as angioid streaks.

TABLE I

Salient Features of Reported Cases

CASE	AUTHOR	AGE SEX	GENERAL MEDICAL FINDINGS	BLOOD PRESSURE	URINE ALBUMIN	VISION		RETINAL PATHOLOGY		EXUDATE	ADDITIONAL OCULAR FINDINGS	OUTCOME	INTERVAL BETWEEN DIAGNOSIS OF STREAKS AND DEATH
						LE	RE	Vessels	Hemorrhage				
1	Siegrist (1)	65 M	Chronic alcoholic, hearing diminished ½ month	0		20/200	20/200	Moderately constricted	—	—	Peripapillary pigment atrophy	Died of generalized arteriosclerosis, autopsy performed, eye pathology reported	7 months
2	Siegrist	50 F	Septic sinus thrombosis 2 years previously, generalized arteriosclerosis								Optic atrophy both eyes		"Lived several years" (Fuchs)
3	Magitot (9)	65 F	Arteriosclerosis hemiplegia		+	20/300	20/300	Arteries normal, veins thickened	+			Died of left hemiplegia, autopsy performed, eye pathology reported	8 months

4	Lindner (3)	58 F	Arteriosclerosis nephrosclerosis	160	+	20/20	20/20	Constricted				Autopsy confirmed medical diagnosis No eye pathology report	Short time
5	Lindner	50 F	Hypertrophy of left side of heart	190	+	CF	CF		−	−	Macular pigment		
6	Lindner	62 F	Asthma and palpitation										
7	Holm (7)	80 F			−	20/100	27/72		−	−	Macular pigment		
8	Koppl (40)	45 F	Nephritis for for 9 years	240	+	20/20	20/140	Constricted	+	+	Macular pigment	Died in 1 month	1 month
9	Koppl (40)	68 F	Enlarged heart	255	+	20/30	20/20				Old central choroiditis	Died in 3 months	3 months
10	Koppl	62 F	Hemiplegia 8 yrs. previously, heart enlarged	230	+	20/25	20/25		+			Died of apoplexy in short time	"Short time"
11	Koppl	34 F	Chronic nephritis	250	+	20/752	20/100	Constricted	+	+	−		

TABLE I—*Continued*

CASE	AUTHOR	AGE SEX	GENERAL MEDICAL FINDINGS	BLOOD PRESSURE	URINE ALBUMIN	VISION		RETINAL PATHOLOGY		EXUDATE	ADDITIONAL OCULAR FINDINGS	OUTCOME	INTERVAL BETWEEN DIAGNOSIS OF STREAKS AND DEATH
						LE	RE	Vessels	Hemorrhage				
12	Koppl	47 F	History of decompensation, enlarged heart	225	+	CF	20/60	−	+				
13	Koppl	63 F	Hemiplegia 1 yr. previously enlarged heart	260		20/20	20/20						
14	Holm (12)	60 M	Chronic nephritis	Increased		20/80	8/200	Constricted	+	+	Retinitis circinata		
15	Holm (12)	44 M	Apoplexy		−	20/200	20/20		+	+	Macular pigment	Died 11 years later of apoplexy (Thordarson)	11 years
16	Fuchs (5)	36 F	Enlarged heart malignant nephrosclerosis	250	+	20/20	20/20	Constricted	+	+	Elschnig foci		

17	Vos and Zeeman (13, 14)	63 M	Essential hypertension	Increased									
18	Burian (6)	M	Arteriosclerosis, decreased intelligence			20/50	20/70						
19	Burian (6)	74 F	Enlarged heart	230	+	CF	CF		+	−	Old choroiditis		
20	Burian (6)	50 F	Enlarged heart	270/160	+	12/200	20/200	−	+	+			
21	Thordarson (8)	F	Hypertension	270/150	−	20/20	20/80	−	−	−			
22	Thordarson	66 M	Hypertension	250	−	30/150	20/150	Prominent	+		Edema of retina		
23	Thordarson	73 M	Hypertension	190	+	20/300	20/300				Central choroiditis		
24	Thordarson	59 F	Hypertension and apoplexy	275/130	−	LP	20/100				Cataract RE atrophic retina		
25	Thordarson	51 F	Nephrosclerosis and hypertension	335/180	+				−	−			

TABLE I—*Continued*

CASE	AUTHOR	AGE SEX	GENERAL MEDICAL FINDINGS	BLOOD PRESSURE	URINE ALBUMIN	VISION		RETINAL PATHOLOGY		EXU. DATE	ADDITIONAL OCULAR FINDINGS	OUTCOME	INTERVAL BETWEEN DIAGNOSIS OF STREAKS AND DEATH
						LE	RE	Vessels	Hemorrhage				
26	Thordarson	61 F	Hypertension, chronic nephritis, cerebral hemorrhage	275/190	−			Constricted			Retinal arteriosclerosis		
27	Thordarson	70 M	Hypertensive cardiovascular renal disease	225/140	+	20/50	20/70				Pigment in macula	Died in 9 days with cerebral hemorrhage, autopsy performed eye pathology reported	9 days
28	Scholz	42 M	Hypertensive cardiovascular renal disease	280/170	+	20/20	20/20	Constricted	+	+	Hypertensive retinopathy	Died in acute cardiac decompensation	9 months
29	Scholz	48 M	Hypertensive cardiovascular renal disease	250/160	+	20/20	20/20	Constricted		+	Early hypertensive retinopathy	Died in acute cardiac decompensation	6 months

30	Scholz	58 F	Hypertensive cardiovascular disease	230/130	+	20/30	No LP	Constricted	−	−	Early hypertensive retinopathy myotic degeneration	Alive 3 years later	Alive 3 years later
31	Scholz	60 M	Hypertensive cardiovascular disease	192/110	+			Constricted	−	−	Early hypertensive retinopathy	Died from cerebral vascular accident	1½ years
32	Scholz	70 M	Hypertensive cardiovascular disease	175/105	+			Constricted			Early hypertensive retinopathy	Died in cardiac decompensation complete autopsy studied	50 days

Key: − = not present, + = present.

Lindner (3), unaware of Siegrist's report, published three case histories and differentiated them from angioid streaks. Koppl (4) observed their occurrence in hypertension with kidney disease and stated that they indicated poor prognosis. A. Fuchs (5) placed them in the group of diseases known as albuminuric choroiditis and discussed their prognostic significance. Burian (6) reviewed the existing cases in 1935.

The reported cases are summarized in Table I. It is difficult to estimate accurately from the literature the extent and duration of the cardiovascular renal disease. Pathological or clinical evidence of cardiovascular disease were found in all of the patients except one of Holms (7). No record of medical examination was given in this case.

The systolic blood pressure was recorded as increased in two cases, 160 and 190 millimeters of mercury in three others, and in the remaining twenty it was over 225 millimeters of mercury. When studied, the heart was reported as enlarged and generalized arterial sclerosis was described. Evidence of kidney damage was reported in twenty-one instances. In five of these the diagnosis of nephritis was made. Albuminuria reported nineteen times, hematuria two times, and elevated blood non-protein-nitrogen, reported in the five cases added here, are the evidence offered for accompanying kidney damage.

Thordarson (8) suggested that because four of his seven cases did not have albuminuria that the streaks develop between the appearance of hypertension and the development of nephrosclerosis. One of his reported cases died nine days after he discovered the streaks. He did not study the remainder of his patients for a period of time.

As can be seen in Table I the cases are predominantly female and mainly in the 5th and 6th decades of life although seven are in the 3rd and 4th decades. No patient had a positive serologic test for syphillis, although syphillis was suspected in Siegrist's first case.

The presence of the streaks in eyes uncomplicated by macular pathology had no effect on the vision. Approximately half of the eyes had normal vision while the remainder had diminished vision because of accompanying macular or retinal pathology. Four reports told of macular pigment, two of old central choroiditis, one of optic atrophy, and one of retinitis circinata.

As Burian pointed out in his excellent review, the majority of the reported cases are myopes. The present survey shows that twelve are

myopic and six hyperopic. In the remaining fourteen the refractive error is not reported.

The retinal vascular tree is described as narrowed in about half of the cases and hemorrhages and exudates are mentioned in a similar number.

The streaks are illustrated as consisting of clumps of pigment deposited serially over partially, but not completely sclerosed choroidal vessels. They appear not unlike a chain of black beads and were called "string of pearls" by Lindner. The deposits usually begin one or two disc diameters below the papilla and extend radially. Occasionally the pigment deposits are seen in the far periphery. That they are present only over partially sclerosed vessels was mentioned by Siegrist in his original communication and borne out by subsequent observations. The choroidal vessel is frequently visible and is accompanied by a wide band of apparently depigmented choroid. The pigment has been described as wreathing the vessels, but in the illustrations appeared to be overlying them. The fundus presents the picture of heavy choroidal sclerosis and in many patients completely occluded choroidal vessels are described. No pigment deposits are seen over these occluded vessels. In Fuchs' case the epivascular choroidal streaks are accompanied by a single Elschnig dot.

Pathological studies: Siegrist in reporting the first case gave a histological report of the autopsy findings. He found a general high grade arteriosclerosis affecting the aorta, coronary and cerebral arteries. Many foci of softening were found in the cerebrum and cerebellum. Atheromatous degeneration was found in many of the larger brain arteries, especially the vertebral arteries.

The eye was sectioned and the retina was described as normal except for insignificant changes in the retinal vessels. The lamina vitrea was also normal. There was a varying amount of sclerosis in the choroid, and over the partially sclerosed vessels there were wart like proliferations of the pigment epithelium. An increase in the pigment content of the cells was apparent. The choroidal vessels over which the pigment proliferations lay showed necrosis of the vascular walls and endarteritis obliterans with hyaline degeneration. Around some of the diseased choroidal vessels some round cell infiltration was noted.

Magitot (9) reported another case with an autopsy report. The

brain showed old widespread softening which had destroyed the posterior half. The cerebral vessels were atheromatous and there was a classic hemorrhagic focus on the right side. The kidney showed cortical atrophy.

The bulbi were not fixed until 24 hours after death and were deformed. Sclerotic vascular changes were found throughout the optic nerve, retina and choroid. The chorio-capillaris was in some areas completely obstructed. Proliferation and thickening of the intima was noted along with some leucocytic inflammation. Magitot stated that the "pigment epithelium appeared to have suffered very little from the angio-sclerotic modifications".

Bayer (10), in reviewing the same preparations saw small accumulations of heaped up pigment cells in the retina which he believed accounted for the ophthalmoscopic appearance.

Thordarson more recently studied histologically an autopsy case. He stated that the retina was normal. There was a proliferation of the pigment over the major choroidal vessels. He did not find any degenerative changes in the walls of the vessels. In addition he found Bruch's membrane broken in places.

DISCUSSION

In considering the fundus picture of this disorder, several distinctive features can be explained pathologically: (1) The character of the pigment spots over the diseased choroidal vessels. (2) The tigroid appearance of the fundus and in particular the light band which accompanies the choroidal vessels over which the pigment spots are located. In addition the differential diagnosis, the fundus picture and the medical prognostic significance of the lesions are to be considered.

Our reconstruction of the pathological picture agrees with that of Siegrist and shows, we believe, that the spots are due to a proliferation of the pigment epithelium over the partially occluded sclerosed choroidal arteries. Because of the location of the pigment as it appears when seen with the ophthalmoscope and because of its anatomical position when studied pathologically it is suggested that this lesion be called epivascular choroidal pigment streaking. Bayer in his restudy of Magitot's material found no changes in the pigment epithelium but attributed the picture to small accumulations of pigment in the retina.

It is difficult to explain why they were unable to explain satisfactorily the fundus lesions.

Many explanations have been offered thus far for the proliferation of the pigment epithelium.

Siegrist raised the question of whether the pigment proliferation was due to either a simple primary hypertrophy or hyperplasia of the pigment epithelium or to a nutritional disturbance caused by a degeneration of the pigment epithelium with a subsequent proliferation of the pigment cells. He was inclined to accept the first view.

Koppl (4) suggests that the high blood pressure leads to necrosis of the vessel walls and that the toxins which duffuse from such necrotic areas set up an irritation which causes an increase in the retinal pigment cells lying along the vessels concerned.

E. V. L. Brown (2b) suggested that in the process of hardening, the vessels may first become relaxed and then distended, thus pressing against the lamina basalis and epithelium and causing a proliferation of the pigment epithelium by the constant pressure.

Voerheeff (2a) suggested that the markedly sclerosed choroidal vessels may pulsate to an unusual degree for a time and that this may locally stimulate the pigment epithelium to proliferate.

Fuchs (5) proposed, but did not demonstrate, that the light areas seen in the periphery of the fundi (such as were illustrated in case 4, (Fig. 2)) were due to spotty sclerosis of the choriocapillaris. He postulated that the pigment proliferation which occurs in Siegrist and Elschnig spots is caused by the same general toxin which causes the hypertension. In the case of the streaks described by Siegrist he believes the process is more generalized, while in the Elschnig spots the process is more localized.

The additional observation made here demonstrating the absence of the choriocapillaries over and in the region immediately adjacent to the pigment choroidal artery offers an adequate explanation for the proliferation of the pigment epithelium and for the light band accompanying the divided artery.

Passero (11) studied in detail the choriocapillaris in man. In the macular region the capillaries of this layer are wide and numerous, accounting for the brilliant solid red color of the macular region. At the equator the choriocapillaris emerges from the arterioles and courses meridionally along the arteries.

A similar observation was made by us on an albino rabbit eye preparation made by Dr. Jonas Friedenwald. The vascular tree of the eye was injected with silver nitrate and then exposed to sunlight. The retina was removed and the specimen mounted whole. Fig. 9 shows the course of the capillaries over a choroidal vessel in a region comparable to where the pigment appears. It is seen that the capillaries course over the choroidal vessel and parallel to it. We have further

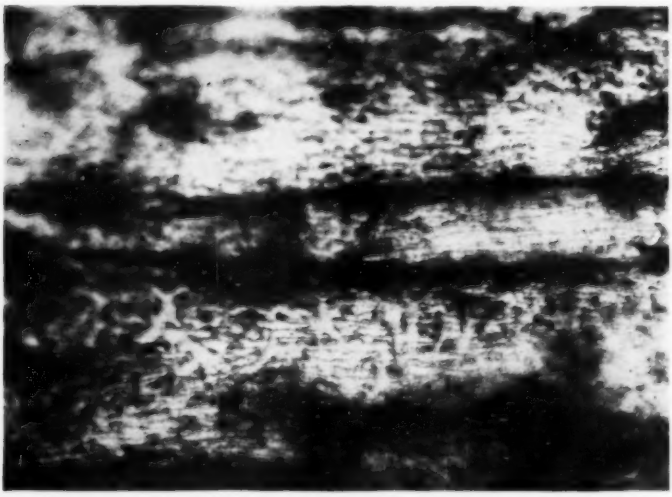

FIG. 9. FLAT PREPARATION OF CHOROID OF ALBINO RABBIT (× 750). VASCULAR TREE INJECTED WITH SILVER NITRATE AND EXPOSED TO SUNLIGHT

Choroid capillaris in area comparable to that in which epivascular choroidal pigment stripes appear. Note meridioneal course of choriocapillaris

described large sclerotic plaques in the artery over which the pigment proliferation took place. These plaques in all probability occlude the arterioles to the choriocapillaris, either directly or by pressure, thus accounting for the occluded choriocapillaris over and adjacent to the artery. It is in this region of the occluded choriocapillaris that ophthalmoscopic examination reveals that the artery is accompanied by a clear band. The pigment epithelium proliferates over the artery in the same area. It seems likely that the disappearance of the pigment epithelium is a consequence of the occlusion of the choriocapil-

laris and that the persistance of the pigment immediately over the artery may be due to the nutritional state being less bad here than at a greater distance away from the arterial blood column. Just what factors are responsible for the proliferation of these persisting cells cannot be specified at present.

The Elschnig spots which are individually somewhat similar in appearance and occur over sclerosed choroidal vessels may be due to the occlusion of the choriocapillaris in a more localized area. The disease process in the former case extends along a whole vessel and in the latter extends to a single efferent arteriole.

Differential diagnosis: The picture of epivascular choroidal pigment streaks is quite disinctive and presents a picture quite unlike that of any other fundus picture which presents streaks. The following are the disorders most frequently confused with epivascular choroidal pigment stripes:

a) Angioid streaks have been most frequently confused in the literature with epivascular choroidal pigment streaks (1, 9, 7). Lindner separated these two types of streaks. Angioid streaks always radiate from a peripapillary ring, have a serrated border and bear no relationship to the retinal or choroidal vascular tree.

b) Pigment streaks following choroidal detachment, may appear somewhat like rosary streaks in that numerous fine beads of pigment are seen. These stripes, however, are always in the periphery of the fundus and do not bear the constant relationship to the choroidal vessels that epivascular choroidal pigment streaks do.

c) Perivascular choroidal pigment atrophy (1e) has no pigment deposit. Instead, there is a zone of depigmentation around the choroidal vessels. None of these patients have hypertension.

PROGNOSIS

It is suggested that the fundus picture usually develops terminally, for in our first patient the pigment streaks were not seen when a complete fundus examination was made one month prior to their discovery. Under our observations the lesion was seen to develop further during the last eight months of the patient's life. In our second case epivascular choroidal pigment streaks were discovered six weeks after examination by a competent observer.

Of the twenty seven cases gathered from the literature and the five

reported here, fourteen give sufficient data to determine the time between the discovery of the fundus picture and the patient's death (Table I).

Three cases, Siegrist's second, Holm's second, and our third, lived longer than one and one-half years after the discovery of the choroidal picture. The remaining cases died within nine days and eighteen months later.

A study of the description of the fundus picture in the literature and in particular from the study of the cases reported here, suggests that the albuminuric retinitis present in these cases was not sufficiently severe to offer so poor a prognosis. It is probable that the choroidal lesion is not only overlooked but is frequently obscured by overlying retinal edema accompanying the albuminuric retinitis. The findings of the epivascular choroidal streaks however, have in all but three occasions been followed by death in a year and a half or less. Therefore, we believe that they are possibly of general medical and prognostic importance.

Three of the four cases reported here were first diagnosed by colleagues who were acquainted a few months previously with our first case and a review of the literature. We feel, therefore, that this lesion is common but has been generally overlooked because of the obscurity of its description. This description of these cases may stimulate further observation of similar patients.

SUMMARY AND CONCLUSIONS

1. Five cases of epivascular choroidal pigment streaks, the pearl or rosary streaks of Siegrist, are reported and the literature is reviewed.

2. All of the reported cases, except one, had hypertensive cardiovascular disease. Evidence of renal involvement was presented in twenty one of the cases.

3. In one of the cases reported here an autopsy including the eyes was studied.

4. It is demonstrated by anatomical reconstruction that the ophthalmoscopic picture is produced by a proliferation of the pigment epithelium over partially sclerosed choroidal arteries. This proliferation and the accompanying light band is probably caused by arterioslerotic lesions which have occluded the efferent arterioles supplying the choriocapillaris over and adjacent to the sclerosed coroidal arteries.

5. In general the cases had a poor prognosis after the discovery of the fundus picture and it is therefore suggested that this sign may be of possible prognostic value.

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THE SIGNIFICANCE OF STREPTOCOCCI ISOLATED FROM THE FEMALE URINARY TRACT

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Our interest in streptococcus infections of the urinary tract was aroused as the result of a study of the organisms occurring in urine cultures from women patients on the Gynecological and Obstetrical Services of the Johns Hopkins Hospital. The incidence of streptococci in this series of 9,052 consecutive cultures, including sterile specimens as well as those from which growth was obtained, is given in Table I.

Besides the large number of streptococci occurring in these cultures perhaps the most significant finding is the relative incidence of the various serologic groups of beta hemolytic streptococci. It is the Group A beta streptococci which are highly pathogenic for man, the cause of the acute and severe streptococcus infections and the most frequently isolated from clinical material. In our series the relative incidence of these organisms is the reverse of what might be expected. This is illustrated in Table II, in which the incidence of the various serologic groups of beta streptococci in urine and throat cultures is compared. These findings raised the question as to the significance of streptococci in relation to urinary tract infection.

A preliminary inquiry indicated that no adequate study of streptococcus infections of the urinary tract has been made. Therefore it seemed appropriate at this time to study the case histories of the patients from whom these organisms had been isolated in order that the pathogenicity of the various streptococci in the female urinary tract might be determined.

REVIEW OF THE LITERATURE

A review of the literature since 1939, after which time the serological grouping of beta streptococci became a fairly common laboratory procedure, has revealed very little information concerning streptococcus infections of the urinary tract. Everett (2) in his recent book on

TABLE I

Occurrence of Streptococci in 9,052 Consecutive Urine Cultures from Women on the Gynecological and Obstetrical Services

SERVICE	BETA STREPTOCOCCI						ALPHA STREPTOCOCCI*	GAMMA STREPTOCOCCI*	ALPHA† AND GAMMA ENTEROCOCCI	MICROAEROPHILIC STREPTOCOCCI	TOTAL NUMBER OF STREPTOCOCCI
	Group A	Group B	Group C	Group D	Group not determined	Total number of beta streptococci					
Gynecology	3	47	14	33	10	107	256	18	454	15	850
Obstetrics	0	17	0	6	1	24	57	12	124	2	219
Totals	3	64	14	39	11	131	313	30	578	17	1,069
Percentage of total number of cultures	0.03	0.7	0.15	0.43	0.12	1.45	3.46	0.33	6.39	0.19	11.81
Percentage of total number of streptococci	0.3	6.0	1.3	3.7	1.0	12.3	29.3	2.8	54.0	1.6	100

* Other than enterococci.

† Usually referred to as *Streptococcus fecalis*.

TABLE II

Relative Incidence of the Serological Groups of Beta Hemolytic Streptococci in Urine and Throat Cultures

SEROLOGICAL GROUP OF BETA HEMOLYTIC STREPTOCOCCI	OCCURRENCE IN URINE CULTURES		OCCURRENCE IN THROAT CULTURES*	
	Number of strains	Percentage†	Number of strains	Percentage†
Group A	3	2.2%	220	84.6%
Group B	64	48.8	18	7.0
Group C	14	10.6	16	6.1
Group D	39	29.7	—	—
Group not determined	11	8.4	6‡	2.3
Total number of strains	131	100%	260	100%

* From the Bureau of Bacteriology of the Maryland State Department of Health (1).

† Percentage of the total number of beta streptococci.

‡ These strains were not tested against Group D antiserum.

Gynecological and Obstetrical Urology reports the incidence of streptococci in 1,000 consecutive cultures of bladder urine from the Gynecological Cystoscopic Clinic of the Johns Hopkins Hospital. In his series he found 4 strains of Group B beta streptococci and 71 cultures from which *Streptococcus fecalis*[1] was isolated. No other streptococci occurred in this series. In 148 kidney cultures *Streptococcus fecalis* occurred in 29 or 19.6% of the cases and alpha streptococci in 17 or 3.4% of the cases. Beta streptococci from this source, Everett states, occur with great rarity.

In a publication by Marple (3) the results and clinical significance of urine cultures from 100 unselected patients in a women's ward have been analysed. Sixty-three of these patients had consistently negative cultures. Streptococci were isolated from 12 of the cases with positive cultures. These organisms were identified as one Group B and one Group D beta streptococci, both from patients with urinary tract infections, and 3 unidentified beta hemolytic streptococci, 2 of which were from patients with no symptoms referrable to the urinary tract. Six strains are reported simply as "*Streptococci viridans*", 3 of which were isolated from patients with pyuria and 3 from doubtful urinary tract infections. The twelfth streptococcus was not identified and was isolated from a patient with pyuria.

In a series of papers Long and Bliss (4, 5, 6, 7, 8, 9) report a total of 8 cases of urinary tract infections caused by Group B beta hemolytic streptococci, 10 Group D infections, 2 alpha streptococci and 1 gamma *Streptococcus fecalis*. Their largest series comprises 57 cases of which 6 were caused by Group D beta streptococci and one by gamma *Streptococcus fecalis*.

Helmholz (10, 11, 12, 13, 14, 15, 16, 17, 18) in a number of reports on urinary tract infections and in vitro studies on organisms isolated from such infections mentions only *Streptococcus fecalis*. Although no specific incidence of infection is given he includes *Streptococcus fecalis* in all lists of organisms frequently isolated from urine cultures. Poole and Cook (19) in 50 cases of urinary tract infection report 7 caused by *Streptococcus fecalis* but no other streptococci were found. Cook (20),

[1] Throughout most of the literature quoted all alpha and gamma enterococci are included under *Streptococcus fecalis*. Probably most of them were *Streptococcus fecalis*. *Streptococcus liquefaciens* is not reported as such.

reporting 200 cases, gives no figures on the incidence of the various organisms involved but mentions *Streptococcus fecalis* as being one of the causative organisms in this series. In another publication Cook (21) again includes *Streptococcus fecalis* as among the common causes of urinary tract infections but reports no specific number of cases. Greene, Poole and Cook (22) describe 42 cases, again including *Streptococcus fecalis* as one of the etiological agents involved but mention no other streptococci. The same is true of the reports of Herrold (23) and Poole (24). One cannot help but infer from these papers that *Streptococcus fecalis* is the only streptococcus of any significance in urinary tract infections.

Goldstein (25) studied the pathogenicity of *Streptococcus fecalis* in the urinary tract of rabbits. He reports that, although the organisms is far less pathogenic than staphylococci, using a small inoculum *Streptococcus fecalis* produced pyelitis with rare abscess formation in 37% of the rabbits and if a large inoculum were used in 100% of the experimental animals. Goldstein concludes from these experiments that *Streptococcus fecalis* isolated from the urinary tract may be considered of etiologic significance.

Young, Colston and Hill (26), in 600 cases of urinary tract infection in males, report 67 cases in which streptococci were involved, 30 of them in pure culture. The organisms, however, were not further differentiated. Vest, Hill and Colston (27) cover a series of 109 cases which included 2 caused by beta hemolytic streptococci, the serological groups of which were not determined, 16 alpha hemolytic streptococci, 6 gamma streptococci and one unidentified streptococcus. Culp (28) reports 2 strains of alpha *Streptococcus mitis* and 4 strains of *Streptococcus fecalis* occurring in 24 cases. Young, Hill, Jewett and Satterthwaite (29) found 5 strains of *Streptococcus fecalis* occurring in 29 cases and Satterthwaite, Hill and Young (30) in 54 cases report 1 alpha *Streptococcus ignavus*, 2 alpha and 1 gamma *Streptococcus fecalis* and 1 unidentified streptococcus. These reports are particularly interesting in that of the total number of 212 cases of urinary tract infection in which the streptococci isolated therefrom were differentiated, only 2 cases involving beta hemolytic streptococci were found.

Porch (31) studied 100 strains of streptococci isolated from urine

specimens (from males) from a purely bacteriological standpoint, making no clinical correlation with the case histories of the patients. She reports that 24 of these organisms were alpha hemolytic streptococci, identified specifically as 10 strains of *Streptococcus equinus*, 7 *Streptococcus mitis*, 2 *Streptococcus fecalis* and 2 *Streptococcus salivarius*. The remaining 76 strains she identified as gamma streptococci, 73 of which were found by cultural characteristics to be enterococci. These enterococci she reports as 70 strains of gamma and delta *Streptococcus fecalis* and 3 strains of gamma *Streptococcus liquefaciens*. The remaining 3 strains which proved not to be enterococci Porch reports also as gamma *Streptococcus fecalis*. No beta streptococci are included in the series and the author states that "beta streptococci from this source (i.e., urine cultures) have been extremely rare".

In the light of our experience with the varied organisms to be found in urinary tract infections the publications of Alyea and his co-authors are very difficult to interpret. Alyea (32) reports a series of 400 cases, Alyea and Roberts (33) 208 cases, Alyea and Stuart (34) 250 cases and Alyea and Parrish (35) 152 cases, a total of 1,010 cases. In this large series of urinary tract infections the organisms involved are consistently differentiated into three large groups, colon bacilli, staphylococci and mixed cultures, or occasionally they are referred to more specifically as *E. coli*, *Staphylococcus aureus* and mixed infections. No streptococci or any other organisms of any kind are mentioned, although in the text *Streptococcus fecalis* infections of the urinary tract are occasionally referred to.

Neter and Short (36) found 13 streptococci in 43 cases of urinary tract infection but only one, alpha *Streptococcus salivarius*, was specifically identified in the report. In in vitro experiments on streptococci isolated from the urinary tract Neter (37, 38, 39) refers to the organisms as "hemolytic and non-hemolytic enterococci" and no more specific identification is given.

Other publications have yielded no more information concerning the incidence and significance of streptococci in the urinary tract. A number of other clinical reports have been reviewed but except for an occasional reference to *Streptococcus fecalis* no further information concerning streptococci in urine cultures could be obtained. It should be noted, however, that in all reports there is no mention of the occur-

rence of a single strain of Group A beta hemolytic streptococci. This omission is in line with our findings as shown in Table I.

This review of the literature has clearly shown that, with the exception of *Streptococcus fecalis*, that is, the alpha and gamma enterococci, the relation of streptococci to urinary tract infections has received little attention. It has also shown that in many reports the organisms have not been sufficiently identified but have been reported in general descriptive terms only, as, for instance, a "hemolytic streptococcus." The information contained in such reports is, therefore, difficult to evaluate. Few of the papers included a description of the methods used in the isolation and identification of the organisms. For this reason it is impossible to determine if, in the large series of cases in which no streptococci were reported, cultural methods were used which would have demonstrated the presence of these organisms. In consideration of these facts we feel that a study such as we have undertaken will be of value.

BACTERIOLOGICAL METHODS

The streptococci reported in this paper were isolated from catheterized urine specimens in the course of the ordinary laboratory routine. The methods used for the isolation and identification of these organisms were those described by Schaub and Foley in *Methods for Diagnostic Bacteriology* (40). The procedure of Brown (41) was used for the serological grouping of the beta streptococci. The strains which failed to react with Group A, B, C and D antisera have been classified as "streptococci—group not determined". It is possible that they were of a serological group for which no serum was available. In all doubtful instances the serologic grouping was checked by a cultural study of the organisms.

The serologic Group D streptococci of intestinal origin are collectively known as enterococci (Sherman, 42; Brown and Schaub, 43). These organisms are remarkable clinically for their resistance to sulfonamide therapy (Bliss and Long 7, 8; Helmholz 10, 12, 13, 17, 18; Cook 20, 21; Herrold 23; Poole 24; Culp 28; Neter 38, 39; Alyea and Roberts 33; and many others). On blood agar they may produce either the alpha, beta or gamma appearance. In this paper the beta hemolytic strains have been grouped serologically as described above and reported as Group D beta streptococci. The alpha hemolytic

strains of enterococci and those producing gamma type colonies have been reported as such. In the literature these have generally been referred to as *Streptococcus fecalis*.

Streptococci producing the alpha or gamma appearance in blood agar, exclusive of those regarded as enterococci as described above, have been reported as alpha streptococci or gamma streptococci as the case may be. The micro-aerophilic streptococci included in this report are those which grew well in aerobic broth cultures and on anaerobic blood agar plates but which failed to grow aerobically on blood agar.

CLINICAL STUDY OF PATIENTS FROM WHOM STREPTOCOCCI WERE ISOLATED

For the clinical study of the cases from which streptococci had been isolated those occurring on the Gynecological Service were selected. As shown in Table I, 850 strains of streptococci were recovered from these patients. The survey has been limited to 500 cases for which histories were readily available. The occurrence of the various streptococci of these cases is given in Table III.

The histories of these patients were reviewed for information concerning the source of the streptococcus, whether bladder, kidney or both, the occurrence of the streptococcus with other organisms, and especially for signs and symptoms referable to urinary tract infection. From this information the probable significance of the organism was determined. The results of this study will be discussed under the various types of streptococci occurring in urine cultures.

An apparent discrepancy in our results should be explained here. Organisms listed in our tables as isolated from patients with cystitis or pyelitis have occasionally been regarded as of doubtful significance. These were cases in which the symptoms were referable to some other infection or condition, for example, tuberculosis of the urinary tract, interstitial cystitis or Hunner's ulcer.

Significance of Group A Beta Hemolytic Streptococci

Group A beta hemolytic streptococci were isolated from 3 of the 9,052 urine cultures, an incidence of only 0.03%. Histories were available on only two of the patients from whom these isolations had been made. One of these strains was isolated in pure culture from the bladder of a patient with no clinical symptoms of urinary tract disease.

No explanation of the presence of the organism in this culture can be given. The second strain of Group A beta streptococci occurred in mixed culture with *Staphylococcus albus* in the bladder urine of a patient with symptoms of cystitis. A previous culture had also shown *Staphylococcus albus;* a later culture was sterile. The significance of the streptococcus in this case is debatable as it might or might not have been etiologically involved with the staphylococcus.

TABLE III

Occurrence of the Various Types of Streptococci in the 500 Cases Included in This Report

STREPTOCOCCUS	NUMBER OF STRAINS
Beta streptococci	
Group A	2
Group B	33
Group C	12
Group D	21
Group not determined	8
Total number of beta streptococci	76
Alpha streptococci	150
Gamma streptococci	15
Alpha and gamma enterococci	252
Microacrophilic streptococci	
Alpha	—
Beta	1
Gamma	6
Total number of microacrophilic streptococci	7

On the basis of these two inconclusive cases no opinion can be offered concerning the significance of Group A beta streptococci in the urinary tract. The low incidence of the organism in the total number of urine cultures, however, certainly suggests that it is rarely found either as a definite etiological agent in urinary tract infections or as one of the streptococci, as frequently found in the other series of cases to be discussed, whose significance is not known.

Significance of Group B Beta Streptococci

Histories were reviewed of 33 of the 64 patients from whose urine cultures Group B beta streptococci had been isolated. As shown in

Table IV, 24 strains of these organisms were isolated in pure culture from the bladder and of these cases 13 showed symptoms of cystitis. The remaining 11 strains were isolated from patients in which no symptoms of urinary tract infection were evident. Nine strains of Group B beta streptococci were involved with other organisms, eight of these occurring in bladder urine. Symptoms of cystitis were present in 5 of these patients and symptoms of pyelitis in one. Two were isolated from cases with no clinical symptoms of urinary tract disease. The ninth strain was obtained in mixed cultures from both bladder and kidney of a patient who was free from urinary tract symptoms, but who had white blood cells in the urine.

From a study of these cases it appeared, as summarized in Table XII, that of the beta streptococci of serologic Group B, 13 were the sole cause of urinary tract infections, 6 were involved with other organisms in such infections and 1 was of doubtful significance. The remaining 13 strains were from patients with no symptoms referable to the urinary tract. The probable significance of these organisms will be discussed later.

Significance of Group C Beta Streptococci

Seventeen strains of Group C beta hemolytic streptococci were found, 0.15% of the total number of cultures and 1.3% of the streptococci isolated. Histories were reviewed of 12 of these patients. In Table V will be found the incidence of Group C beta streptococci in relation to urinary tract disease. Six of these organisms were isolated in pure culture from the bladder, 3 of these from patients with cystitis and 3 from women whose only suggestive symptom or sign was the presence of white blood cells in the urine. One strain was found in pure culture in specimens from both bladder and kidney. This patient, however, had no symptoms of infection but had leucocytes in the urine. In 5 instances Group C beta streptococci were isolated in mixed culture from bladder specimens. One of these patients had symptoms of cystitis, the remaining 4 had no clinical evidence of urinary tract disease.

In appraising the significance of these streptococci (Table XII) 6 were found to be the sole cause of infection, 1 was involved etiologically with other organisms, 1 was of doubtful significance and 4 were isolated from patients with no signs or symptoms referable to the urinary tract.

Significance of Group D Beta Streptococci

Group D beta hemolytic streptococci belong to the enterococcus group described by Sherman (42). Histories were reviewed of 23 of the 33 patients from whom these organisms had been isolated. As shown

TABLE IV

Relation of Group B Beta Streptococci to Urinary Tract Symptoms

OCCURRENCE	SOURCE	WITHOUT SYMPTOMS		SYMPTOMS OF CYSTITIS	SYMPTOMS OF PYELITIS	TOTAL NUMBER OF STRAINS
		Without white blood cells	With white blood cells			
In pure culture	Bladder	11	—	13	—	24
	Kidney	—	—	—	—	—
	Both	—	—	—	—	—
Involved with other organisms	Bladder	2	—	5	1	8
	Kidney	—	—	—	—	—
	Both	—	1	—	—	1
Total Number of Strains.....		13	1	18	1	33

TABLE V

Relation of Group C Beta Streptococci to Urinary Tract Symptoms

OCCURRENCE	SOURCE	WITHOUT SYMPTOMS		SYMPTOMS OF CYSTITIS	SYMPTOMS OF PYELITIS	TOTAL NUMBER OF STRAINS
		Without white blood cells	With white blood cells			
In pure culture	Bladder	—	3	3	—	6
	Kidney	—	—	—	—	—
	Both	—	1	—	—	1
Involved with other organisms	Bladder	4	—	1	—	5
	Kidney	—	—	—	—	—
	Both	—	—	—	—	—
Total number of strains.....		4	4	4	—	12

in Table VI, 12 strains occurred in pure culture from the bladder, 2 of these from cases of cystitis, 3 from patients with symptoms of pyelitis and 7 from women with no symptoms referable to the urinary tract.

Of the 9 strains which occurred in mixed culture, one was isolated from both bladder and kidney of a patient with white cells in the urine

but no urinary tract symptoms. The remaining 8 mixed cultures were present in specimens from the bladder, 3 from patients with symptoms of cystitis, one from a case of pyelitis and 4 from patients with no evidence or urinary tract infection.

As summarized in Table XII, a study of the histories of these patients revealed that 4 strains of Group D beta streptococci were solely responsible for infections of the urinary tract, 3 were involved with other organisms in such infections and 3 were of doubtful significance. Eleven strains occurred in women with no clinical evidence of urinary tract disease.

TABLE VI

Relation of Group D Beta Streptococci to Urinary Tract Symptoms

OCCURRENCE	SOURCE	WITHOUT SYMPTOMS		SYMPTOMS OF CYSTITIS	SYMPTOMS OF PYELITIS	TOTAL NUMBER OF STRAINS
		Without white blood cells	With white blood cells			
In pure culture	Bladder	7	—	2	3	12
	Kidney	—	—	—	—	—
	Both	—	—	—	—	—
Involved with other organisms	Bladder	4	—	3	1	8
	Kidney	—	—	—	—	—
	Both	—	1	—	—	1
Total number of strains.....		11	1	5	4	21

Significance of Beta Streptococci—Group Not Determined

In the 11 cases in which beta streptococci of undetermined group were found, 8 histories were reviewed. In all of these cases the organisms were isolated from the bladder, 7 of them in pure culture. Three of the patients had no symptoms of urinary tract infection and no white cells in the urine, one case was without symptoms but showed white cells, whereas two had symptoms of cystitis and one of pyelitis. The one case in which the streptococci occurred in mixed culture had a definite cystitis. These results are shown in Table VII. As may be seen in Table XII, in 3 instances these organisms were the sole cause of infection, in one they were involved with other bacteria, in another the rôle of the organism was doubtful and in three cases these streptococci were of no apparent significance.

Significance of Alpha Streptococci

Alpha streptococci exclusive of the enterococcal strains were isolated from 313 or 3.46% of the urine specimens and comprised 29.3% of the total number of streptococci found. Histories were reviewed of 150

TABLE VII

Relation of Beta Streptococci, Group Not Determined, to Urinary Tract Symptoms

OCCURRENCE	SOURCE	WITHOUT SYMPTOMS		SYMPTOMS OF CYSTITIS	SYMPTOMS OF PYELITIS	TOTAL NUMBER OF STRAINS
		Without white blood cells	With white blood cells			
In pure culture	Bladder	3	1	2	1	7
	Kidney	—	—	—	—	—
	Both	—	—	—	—	—
Involved with other organisms	Bladder	—	—	1	—	1
	Kidney	—	—	—	—	—
	Both	—	—	—	—	—
Total number of strains.....		3	1	3	1	8

TABLE VIII

Relation of Alpha Streptococci to Urinary Tract Symptoms*

OCCURRENCE	SOURCE	WITHOUT SYMPTOMS		SYMPTOMS OF CYSTITIS	SYMPTOMS OF PYELITIS	TOTAL NUMBER OF STRAINS
		Without white blood cells	With white blood cells			
In pure culture	Bladder	37	—	31	11	79
	Kidney	3	2	—	4	9
	Both	—	—	1	1	2
Involved with other organisms	Bladder	24	4	22	7	57
	Kidney	—	—	1	1	2
	Both	—	—	1	—	1
Total number of strains.....		64	6	56	24	150

* Exclusive of the enterococci.

of these cases. In this series, 64 patients were without signs or symptoms of urinary tract disease and 6 were asymptomatic but white cells were found in the urine. Fifty-six patients had definite symptoms of cystitis and 24 of pyelitis. The occurrence of these organisms in relation to urinary tract symptoms is shown in Table VIII.

Careful review of these individual histories made it evident, as shown in Table XII, that in 41 cases the alpha streptococci could be incriminated as the sole cause of disease and in 33 instances they were involved with other organisms. In 15 of the patients studied the significance of the organisms was doubtful and in 61 no clinical evidence of urinary tract disease was present.

Significance of Gamma Streptococci

Gamma streptococci exclusive of those identified as enterococci were isolated in only 30 cases. Histories were reviewed of 15 of these pa-

TABLE IX

Relation of Gamma Streptococci to Urinary Tract Symptoms*

OCCURRENCE	SOURCE	WITHOUT SYMPTOMS		SYMPTOMS OF CYSTITIS	SYMPTOMS OF PYELITIS	TOTAL NUMBER OF STRAINS
		Without white blood cells	With white blood cells			
In pure culture	Bladder	5	—	—	—	5
	Kidney	1	—	—	1	2
	Both	—	—	—	—	—
Involved with other organisms	Bladder	1	2	3	1	7
	Kidney	—	1	—	—	1
	Both	—	—	—	—	—
Total number of strains.....		7	3	3	2	15

* Exclusive of the enterococci.

tients. In Table IX will be found the distribution of these streptococci according to urinary tract symptoms. In no case was it believed to be the sole cause of infection, in 8 instances it was involved with other organisms and in 7 patients no evidence of clinical disease of the urinary tract could be found. See Table XII.

Significance of Alpha and Gamma Enterococci

The alpha and gamma enterococci, referred to as *Streptococcus fecalis* by most authors, together with the serologic Group D beta streptococci comprise the enterococcus group of Sherman (42). They are of intestinal origin and are of particular interest because of their resistance to sulfonamide therapy. There were 478 cases in which the alpha and

gamma enterococci occurred. They represent 6.39% of the total number of urine cultures and 54% of the streptococci isolated. The frequency with which these enterococci were isolated is in accord with the findings of other investigators, since our review of the literature has indicated that they are generally regarded as among the organisms commonly associated with urinary tract disease.

In Table X will be found the differentiation as to urinary tract symptoms of 252 patients from which these streptococci were isolated. Histories of these patients were studied carefully and it was determined

TABLE X

Relation of Alpha and Gamma Enterococci to Urinary Tract Symptoms

OCCURRENCE	SOURCE	WITHOUT SYMPTOMS		SYMPTOMS OF CYSTITIS	SYMPTOMS OF PYELITIS	TOTAL NUMBER OF STRAINS
		Without white blood cells	With white blood cells			
In pure culture	Bladder	64	7	33	11	115
	Kidney	4	1	2	2	9
	Both	2	—	1	5	8
Involved with other organisms	Bladder	35	12	40	19	106
	Kidney	—	—	—	2	2
	Both	—	1	—	11	12
Total number of strains.....		105	21	76	50	252

that in 58 cases alpha and gamma enterococci were the sole cause of infection. In 88 cases these streptococci were involved with other organisms, in 8 cases their significance was doubtful and in 98 cases there was absolutely no clinical evidence of urinary tract disease.

Significance of Microaerophilic Streptococci

The microaerophilic streptococci occurred in 17 cases or 0.19% of the total number of urine cultures and represent 1.6% of the streptococci isolated. Of these cases 7 were studied. It was found that only 3 strains occurred in pure culture from the bladder, one of these from a case of cystitis and 2 from patients with no urinary symptoms. The remaining 4 streptococci were in mixed culture, 3 from the bladder of patients with symptoms of cystitis and 1 from the kidney of a case of pyelitis.

As shown in Table XII, in only one case were microaerophilic streptococci incriminated as the sole cause of the symptoms. In 4 patients they were involved with other organisms and in two no urinary tract symptoms or signs were present.

Occurrence of Alpha and Gamma Enterococci with Escherichia coli

It has long been our impression that alpha and gamma enterococci are often associated with *Escherichia coli* in urinary tract infections, either occurring with *E. coli* or frequently appearing after the bacillus has been eliminated from the urinary tract.

TABLE XI

Occurrence of Alpha and Gamma Enterococci with Escherichia coli

STREPTOCOCCUS	TOTAL NUMBER OF STRAINS STUDIED	OCCURRED WITH E. COLI	FOLLOWED E. COLI INFECTION	NOT ASSOCIATED WITH E. COLI	PERCENTAGE INVOLVED WITH E. COLI
Alpha and gamma enterococci	252	33	23	196	22.2
Alpha streptococci	150	8	11	131	12.7
Beta streptococci	76	3	—	73	4.0
Gamma streptococci	15	3	3	9	40.0
Microacrophilic streptococci	7	1	—	6	14.3
Total number of strains	500	48	37	415	100

In the instances in which the enterococci were isolated from the urine specimens only after the bacillus had disappeared from the cultures it is probable that the streptococcus was present along with the E. coli in the earlier culture but was overgrown by the E. coli. In the light of our experience with the difficulty in isolating Gram positive cocci when present in small numbers along with a heavy growth of Gram negative bacilli this assumption seems entirely logical. Although mention of this association has been found in the literature (Helmholz 12, 17, 18; Porch 31; Culp 28; and Neter 39), we have been unable to find statistics on the frequency of this relationship between these organisms. It seemed important, then, to review our cases with this in mind. The results of this study are found in Table XI. Here it is shown that in 22% of the cases from which alpha and gamma enterococci were isolated, *E. coli* was also present, either in the same

culture or in a preceding one. On the other hand, in only 12.7% of the cases of alpha streptococcus infection and 4% of the beta streptococcus cases did *E. coli* similarly occur. In the small series from which gamma streptococci were isolated, *E. coli* was also involved in 40% of the cases, and in 14.3% of the cases from which microaerophilic streptococci were isolated this association of the two organisms was found. We have not made a study of the *E. coli* infections to discover in what percentage of those cases streptococci have been isolated, but it does seem clear that in our series the percentage of strains of alpha and gamma enterococci occurring together with or immediately following *E. coli* is significantly greater than that of the other streptococci with the exception of the gamma streptococci.

DISCUSSION

In Table XII is summarized the probable significance of streptococci in 500 instances in which these organisms were isolated from the female urinary tract. Of these 126 or 25.2% were regarded as the sole cause of disease and 144 or 28.8% as involved with other organisms. Thus a total of 270 strains or 54% of the total number of streptococci studied were of etiological importance. In only 31 of the clinical cases, 6%, was the rôle of the streptococcus in doubt.

Perhaps the most interesting finding is the fact that 200 strains or 40% of these streptococci were isolated from patients with no symptoms or signs of urinary disease. This percentage is fairly constant for each type of streptococcus as shown in Table XII.

The significance of the occurrence of this high percentage of streptococci in urine of patients with no clinical evidence of urinary disease is not known. It seems reasonable to presume that frequently they may represent urethral contamination. The normal distribution in the body of streptococci and their relative pathogenicity for man has recently been discussed by Brown and Schaub, (43, 44). Considering the fact that these organisms other than the Group A beta hemolytic streptococci are opportunist pathogens and are normally found in the human intestines and vagina, the assumption that in urine streptococci may represent urethral contaminants seems plausible.

In a number of cases in our series the same streptococcus was isolated on several occasions from patients with no urinary tract disease.

One example may be cited. In this case the patient, who had essential hypertension, was given a complete urinary tract study. From specimens of urine from bladder and kidneys on five different occasions an alpha hemolytic enterococcus was isolated, but to the present date no signs or symptoms of urinary tract disease have been discovered.

TABLE XII

Significance of the Various Streptococci Occurring in Urine Cultures

STREPTOCOCCUS	SOLE CAUSE OF INFECTION	INVOLVED WITH OTHER ORGANISMS	OF DOUBTFUL SIGNIFICANCE	NO EVIDENCE OF INFECTION	
				Number of strains	Percentage*
Beta streptococci					
Group A	—	—	1	1	50
Group B	13	6	1	13	42
Group C	6	1	1	4	33
Group D	4	3	3	11	52
Group not determined	3	1	1	3	37
Alpha streptococci	41	33	15	61	40
Gamma streptococci	—	8	—	7	46
Alpha and gamma enterococci	58	88	8	98	39
Microacrophilic streptococci	1	4	—	2	29
Total number of strains	126	144	30	200	
Percentage of total number of strains	25.2%	28.8%	6.0%	40%	

* Percentage of the number of strains of that species.

The isolation of streptococci on repeated occasions from patients with no urinary symptoms suggests that these organisms may be found over a period of time as apparently harmless inhabitants of the upper or lower urinary tract. It is possible that these streptococci may have been the cause of a past disease or may be responsible for future exacerbations of urinary symptoms. From a study of the histories, however, no etiologic significance could be attached to the streptococci cultured from these cases.

In Table II appears the relative incidence of the various serologic groups of beta hemolytic streptococci isolated from urine cultures as

compared with those from the throat. A marked difference was noted in that the great majority of the beta streptococci from throats were of serologic Group A whereas the largest numbers from urine cultures were of serologic Groups B and D. Only a very small percentage of Group A beta streptococci, which is the group most pathogenic for man, was isolated from urine specimens. It seems logical to presume, therefore, that the urinary tract is not a common focus of Group A beta hemolytic streptococcus infection. It may be that the presence in the urinary tract of beta streptococci other than those of serologic Group A may pave the way for the invasion of other organisms but we have no scientific evidence on this point.

SUMMARY AND CONCLUSIONS

1. The incidence of the various streptococci in 9,052 urine cultures has been determined.

2. A significant difference from that in other clinical material has been noted in the occurrence of the various serologic groups of beta streptococci. As an example is given the incidence of Group A beta streptococci in throat cultures, where it is most common, as compared to that in urine cultures, where it is rarely found.

3. In agreement with other investigators, alpha and gamma enterococci, called Streptococcus fecalis by most authors, were found to be the streptococci occurring most commonly in the urinary tract.

4. The histories of 500 patients from whose urine specimens streptococci were isolated have been carefully studied from a clinical standpoint and conclusions reached in regard to the significance of the organisms.

5. Streptococci were found to be the sole cause of clinical disease in 25.2% of the cases reviewed and involved with other organisms in 28.8%. In a total of 54% of the cases, therefore, they were regarded as etiologically significant. In 6% of the clinical cases studied the rôle of the streptococcus was doubtful.

6. In 40% of the patients from whose urine streptococci were isolated no clinical evidence of urinary tract disease could be found in the history. The significance of the presence of streptococci in this high percentage of cases has been discussed.

7. The relative occurrence of the various streptococci with *Escheri-*

chia coli was studied and it was determined that the alpha and gamma enterococci were involved with E. coli in a significantly higher percentage of cases than the other streptococci with the exception of the gamma streptococci.

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CLINICAL AND ELECTROCARDIOGRAPHIC RESPONSE TO N-METHYLNICOTINAMIDE CHLORIDE ADMINISTRATION IN MAN

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Goldberger and Turner in 1924 reviewed methods for prevention and treatment of pellagra. These workers postulated that a pellagra preventive factor was present in fresh milk and meats. Furthermore, they cited instances in which ingestion of these products prevented pellagra and aided its recovery (1). This early recognition of anti-pellagra activity in specific foods was later followed by the isolation of nicotinic acid from active liver concentrates and its use in the treatment of canine black tongue (2). Spies et al. reported improvement in mucous membrane lesions twelve hours following nicotinic acid administration in man (3).

Spies and Cooper described the complete clinical syndrome and cited the diagnostic criteria in pellagra in 1937 (4). The nervous syndrome observed in nicotinic acid deficiency states was pictured in 1940 (5). Encephalopathy due to nicotinic acid deficiency and relieved by specific therapy was recognized by Jolliffe and his coworkers (6).

The treatment of pellagra has been effectively carried out with nicotinic acid and its amide since 1937. This therapy has fostered investigations directed toward the absorption, metabolic activities, actions and end product excretion of the above drugs. Various pyridine derivatives have been found to exhibit anti-pellagra activity clinically. Among other agents Grant and Huff (7) found sodium nicotinate and the diethyl amide of nicotinic acid (coramine) to be effective.

At this time all investigators are in agreement that pellagra is not the manifestation of a single vitamin deficiency but appears to be the evidence of multiple avitaminoses with pronounced ectodermal abnormalities. Complete subjective and objective relief from pellagra necessities factors of the B complex other than nicotinic acid (8, 9, 10, 11, 12, 13).

Najjar and Wood first described methods for urinary assay of the

fluorescent substance F2 (14). Najjar and Holt (15) in 1941 described a method for the quantitative analysis of the nicotinic acid stores of the body. They obtained a fluorescent measurable substance from the urine of individuals with normal nicotinic acid stores. This had been previously designated as F_2 substance. It characteristically diminishes proportionately with the nicotinic acid stores of the body. F_2 was found to have chemical and physical properties similar to N-methylnicotinamide chloride (16). Others believe F_2 to be identical to or a labile precursor of N-methylnicotinamide chloride. The administration of 200 milligrams of N-methylnicotinamide chloride to normal individuals is followed by the excretion in 48 hours of an amount of F_2 substance equivalent to 55 milligrams of the original product (17). Najjar et al. (18) reported that N-methylnicotinamide chloride exhibited anti-black tongue activity and used this compound in the prevention and cure of nicotinic acid deficiency states in dogs. Other investigators (19) administered N-methylnicotinamide chloride to a dog in an amount equivalent to 25 milligrams of nicotinic acid per day. They found that their experimental animal could not be relieved of a nicotinic acid deficiency state by the equivalent amount of N-methylnicotinamide chloride. It was their conclusion from the results obtained in this experiment that if N-methylnicotinamide chloride has any biological activity it is of an extremely low potency. Najjar (20) is at the present time doing further experimental work in the use of N-methylnicotinamide chloride as an agent which exhibits anti-black tongue activity. His results should be soon forthcoming.

The presence of a patient with pellagra on the wards of the Johns Hopkins Hospital in January of this year provided us with an opportunity to observe the effect of N-methylnicotinamide chloride administration in man. This permitted us to view several interesting manifestations regarding the efficacy of N-methylnicotinamide chloride particularly in regards to psychomotor, mucous membrane and electrocardiographic responses.

Patient G. J. (J.H.H. #342087) colored male, age 49, unemployed, was admitted to the Johns Hopkins Hospital January 28, 1945 complaining of diarrhoea with urgency, tenesmus, numbness and tingling of all four extremities and pig-

mented, fissured, sore hands and wrists. One week prior to this time he had received second degree burns of both lower legs and a third degree burn of the right heel.

Essentially, his diet had, in the preceding 4 months, consisted mainly of oatmeal and bread with an occasional grapefruit and very rarely a serving of pork. His appetite during this time had become progressively worse and insomnia and vertigo were prominent symptoms. He was a chronic alcoholic.

Physical examination: Temp. 101.6; Pulse 116; Blood pressure 124/70. The patient was a dull apathetic, undernourished colored male appearing much older than his stated age. Marked evidence of weight loss was present. There was a dermatitis of the dorsum of the hands extending back to the wrists. These areas were bilaterally pigmented, fissured, roughened, scaly and in one spot weeping. There were several areas of alopecia on the head. Papillary atrophy of the tongue was marked and its color was of a red purple hue. The legs displayed infected second degree burns. There was a third degree burn of the right heel.

Touch, pain, vibratory and position sensations were impaired in the lower extremities.

Laboratory: Wassermann and Kahn positive. The blood revealed a moderate macrocytic anemia. Leukocyte count was normal with a slight shift to the left in a differential count. Non-protein nitrogen, sugar, chloride, carbon dioxide combining power and cholesterol were normal. Stool and urine examinations were not remarkable. Serum albumin, 2.06 grams %. Serum globulin, 3.75 grams %. There was achlohydria following histamine.

Hospital course: On admission patient was placed on a low vitamin diet consisting of 2 soda crackers, 1 cup of tea, a large serving of polished rice and 3 small pieces of hard candy per meal.

On 1/29/45 and 1/30/45 fasting 4 hour urine specimens showed an absence of any F2 substance.[1] On 1/31/45 the patient was given 20 milligrams of nicotinamide intravenously and the fasting urine excreted in the succeeding 4 hours returned 554 gamma of N-methylnicotinamide chloride, an output well below normal. There was no change in the color of the tongue and the dermatitis for two days after the test dose of nicotinamide. Beginning on 2/2/45, 150 milligrams of N-methylnicotinamide chloride[2] was administered daily.

In the next 5 days the dermatitis improved markedly. The normal red color of the tongue was reappearing and the papillae were seen to begin their regrowth.

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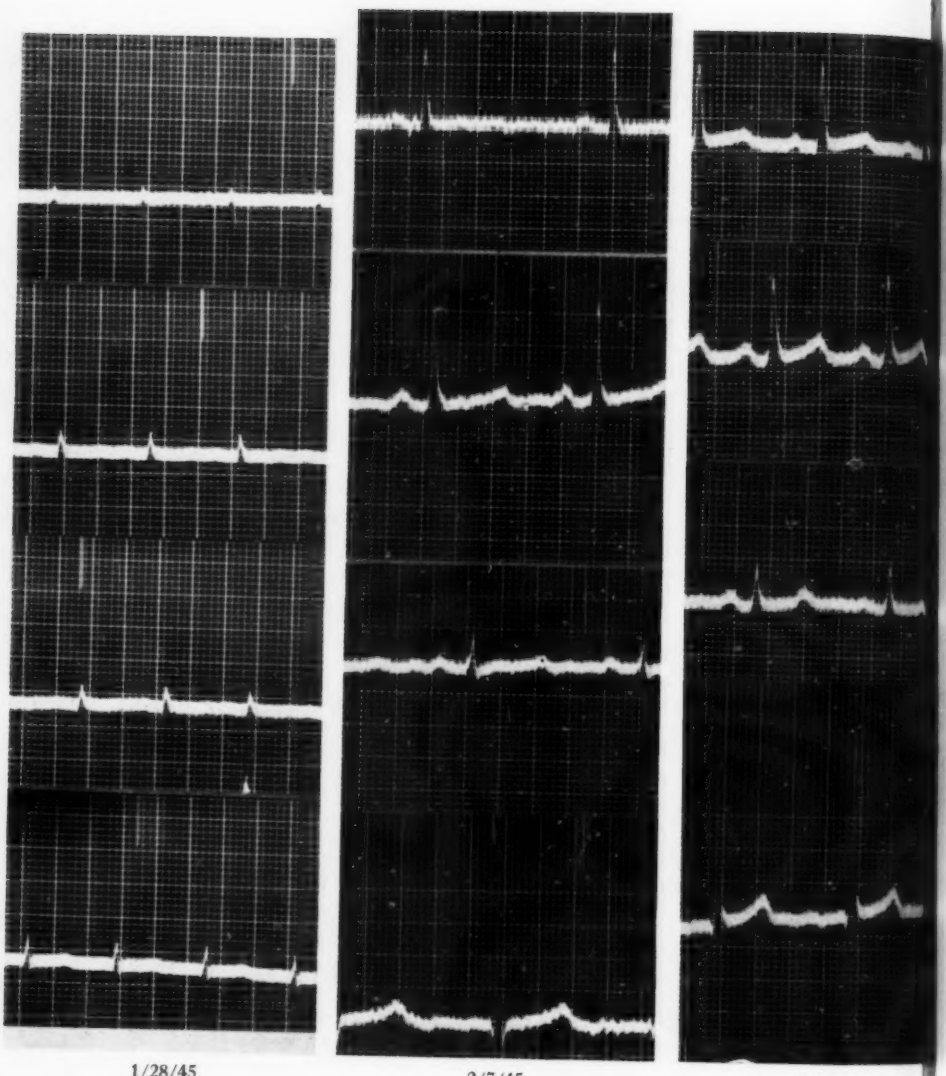
[1] F2 assays on all urine specimens were carried out in the laboratory of the Harriet Lane Home, Johns Hopkins Hospital through the cooperation of Dr. V. A. Najjar.

[2] N-methylnicotinamide chloride was obtained from Taylor & Company, Baltimore, Maryland. Its melting point was 237°C. The melting point of the N-methylnicotinamide picrate was 189°C.



1/28/45 2/7/45 4/19/45

On the other hand, during this same period, the patient began to hallucinate, fabricate and wander aimlessly about the halls. These psychomotor abnormalities responded dramatically in 3 days' time to 50 milligrams of thiamine chloride and 20 milligrams of riboflavin per day.

A normal diet was begun on 2/10/45 and the N-methylnicotinamide chloride therapy was discontinued on 2/13/45. By 3/23/45 his blood picture had reverted entirely to normal but he still had achlohydria following histamine. Serum albumin was 3.5 grams % and serum globulin was 4.06 grams %. Hippuric acid, and bromsulfalein test of liver function were normal.

Unfortunately we were not able to follow the gain in weight exhibited by this patient. This was not possible because of the regime of complete bed rest made necessary by the burns of his lower extremities which eventually required grafting. Just prior to his discharge he was seen by the neurological consultant who found unsteadiness in gait, slight ataxia, absent vibratory sense and diminished position sense bilaterally in the legs. Lumbar puncture because of positive serological tests for syphilis gave a negative Wassermann reaction.

A series of three electrocardiograms was taken on this patient. Below are the electrocardiographic patterns displayed by this patient (1) before therapy (2) following 5 days therapy with only N-methylnicotinamide chloride and (3) just prior to the patient's discharge following adequate diet and added vitamins of the B complex group.

The tracing taken 1/28/45 revealed sinus tachycardia. All limb leads displayed very low voltage in the QRS complex. T1 and T3 were isoelectric. T2 was diphasic. T4 was upright and low. There was no ST segment deviation.

On 2/7/45 following 5 days therapy with N-methylnicotinamide chloride (150 milligrams per day) the EKG revealed a marked increase in QRS voltage. T2 and T3 and T4 were normal. The isoelectric T1 remained the only abnormality.

The final EKG taken on 4/19/45 was within normal limits.

DISCUSSION

Feil studied the electrocardiograms in pellagrins and found T wave inversion and ST segment changes. At the time of his investigation these changes were attributed to thiamine deficiency in as much as this particular deficiency state was previously known to produce cardiac manifestations as well as electrocardiographic abnormalities (21). Porter earlier had described tachycardia as the only abnormal manifestation of cardiovascular activity in nicotinic acid deficiency states (22). Weiss and Wilkins studied the electrocardiographic changes in 67 cases of nutritional deficiency states without elevated blood pressure or clinical evidence of heart disease (23) and found 92.5% of these

patients to exhibit abnormal patterns. The abnormality and their frequencies were:

Change in T wave direction	46
Sinus tachycardia	42
Prolonged QT	53
Ventricular premature beats	10
Auricular premature beats	9
Low QRS voltage	6
Auricular fibrillation	3
Intraventricular block	3

Their patients suffered from clinical pellagra, polyneuritis, psychosis or combinations. They found that the specific clinical syndrome failed to give consistent electrocardiographic abnormalities; nor did all their patients with specific deficiency states have abnormal patterns. Treatment with supplementary vitamins eventually reverted the abnormal tracings to normal electrocardiographic records.

Mainzer and Krause found a high incidence of abnormal electrocardiograms in pellagra. They concluded that though EKG abnormalities occur in pellagra this is not sufficient to state that it is a result of nicotinic acid deficiency alone; however, in some of their cases improvement in the EKG paralleled nicotinic acid administration. Though their cases displaying EKG improvement received nicotinic acid, their patients were not on a so called "pellagra producing" diet (24). Rachmilewitz and Brown reported the effects of nicotinic acid supplements plus an adequate diet on the electrocardiogram in two pellagrins. In their patients they found T waves to be isoelectric in lead I and flat in leads II–III–IV. Following 2 weeks therapy with high caloric diet and supplementary nicotinic acid their patients' EKGs were reverted to normal (25).

QRS and T voltage decrease is seen in diffuse myocardial disease and may also be seen in localized disease. QRS voltage decreases, though not invariably, with alteration in the normal physiological processes in action in the myocardium. The cardiac muscle is functionally abnormal as manifested by low QRS complexes and T waves in some convalescent states from infectious diseases, coronary sclerosis, during myocardial failure, myxoedema, occasionally in cachectic states and rarely in lobar pneumonia, anemia, pulmonary tuberculosis and bronchial asthma. Extra cardiac pathological states by impairing

impulse conduction act to produce similar changes. Pericardial effusion, emphysema and primary or metastatic tumors lying adjacent to the heart may give rise to the QRS and T wave changes described above.

Aside from being the anti pellagra vitamin and as such exercising a physiological function, nicotinic acid is a component of coenzymes I-II. Some workers have found diminution of these enzymes in nicotinic acid deficiency states while normal values are found to follow specific vitamin therapy. Sydenstricker (26) has concluded that symptoms and signs of deficiency states are the end results of chemically altered cellular physiology due to the failure of the coenzyme system.

Since (1) coenzymes I–II are essential to normal physiological functions of cells, (2) nicotinic acid amide holds the most important position in the molecule (3) there is a reduction in both nicotinic acid amide and coenzymes I–II in pellagrins and (4) similiar electrocardiographic abnormalities were found in our patient as found in other states with organically altered myocardial cellular metabolism, it appears that pellagra is capable of producing an altered physiological state of the myocardium productive of QRS and T wave voltage reductions indistinguishable from alterations due to the usual organic structural forms of myocardial disease.

SUMMARY

1. A case of pellagra is presented with dermatitis, mucous membrane changes and electrocardiograph abnormalities responding to N-methylnicotinamide chloride in doses of 150 milligrams per day.

2. Psychomotor abnormalities became more abnormal under this regime and required treatment with other members of the B complex.

3. The patient displayed certain EKG changes which apparently responded only to the administration of N-methylnicotinamide chloride because at the same time the patient was kept on a so called "pellagra producing" diet.

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LIPID RESPONSE TO VITAMIN A ADMINISTRATION

A Possible Test for Vitamin A Deficiency

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It has been known for some time that vitamin A has an important influence on the metabolism of lipids. In 1934,[1] it was shown that when vitamin A was given to rats and other animals daily in large amounts, the lipid and cholesterol level of the blood rose to a considerable degree, later falling to its original level even while the high vitamin A intake was being continued. In recent work, this observation was repeated and confirmed and in addition it was noted that in animals previously rendered deficient the rise in lipids was much greater and lasted a longer time.[2] It was suggested at that time that this reaction might be used to recognize deficiency in the human being. It was to test this possibility that the work recorded in this paper was undertaken.

In this paper only the results in infants are reported. In each case, the infant was studied during a preliminary period varying from three or four days to a week or more, during which one or more determination of vitamin A and total lipids were made. Then vitamin A was given in the form of halibut liver oil or percomorph oil, usually 2 cc. per day as long as the period of observation lasted. During this time determinations of vitamin A and total lipids were made every three or four days. Because of the limitations imposed by the necessity for a rapid "turnover" of hospital beds, it was impossible to make as wide a choice of cases or to study them as long as might be desirable. Moreover, the exclusion of cases with pneumonia* limited the number of cases available for a study that had to be carried out principally in the winter. As a result, the study is to be considered a survey of the reaction of the serum lipids to vitamin A administration rather than a test of the proposition that vitamin A deficiency can be recognized by this reaction.

*The cases with pneumonia have already been studied and the results reported.[3]

METHODS

Blood was obtained by venapuncture or by a deep stab in the heel, the latter procedure being found entirely satisfactory. The serum was separated from the clot within a few hours and kept in the refrigerator until the determination was made. The methods of determination of vitamin A and total lipids have been described in a previous communication.[4]

RESULTS

The results are shown in Table I. The initial vitamin A is included but thereafter only the lipid levels are given, since the infants were receiving vitamin A and the vitamin A levels had no significance for the present study. For ease in reading the table the lipid figures that were significantly above the upper limit of "normal" have been printed in heavier type. From an extensive study of serum lipid levels it has been found that this upper limit for infants lies at about 800 mgs. per 100 cc. Accordingly all figures above 800 mgs. are included as significantly above normal.

As may be seen in the great majority there was no great change in lipid level, although in a certain number of cases there did occur a slight rise followed by a return to the previous figure. It is possible that this rise has significance, but the cases are too few for certainty, and the amount of variation in the preliminary period makes it evident that the later changes cannot with certainty be attributed to vitamin A administration. The most that can be said is that an effect of vitamin A on lipids appears to be demonstrable in some infants but that its significance is doubtful.

In contrast to these are four cases in which the lipid rise was marked and lasted a considerable time. (D. H., C. F., F. S., and C. M.). These were all cases in which nutritional deficiencies were present to a marked degree. Moreover, they were all malnourished, and in all, the initial serum vitamin A was absent or extremely low—below 10 micrograms per 100 cc.

There were five cases in which malnutrition was marked, in four of them combined with more or less chronic digestive disturbance but without evidence of deficiency (S. U., V. C., L. W. and E. H.). In three of these there was a definite but temporary lipid rise, in one

TABLE I

Lipid Response to Administration of Vitamin A in Infant

	AGE	INITIAL SERUM VIT. A MICROGRAMS PER 100 CC.	SERUM LIPIDS, MGS. PER 100 CC.									PREPARATION AND DOSAGE	DIAGNOSIS
			Before beginning Vit. A		After beginning administration of Vitamin A 3 day periods								
			1	2	1	2	3	4	5	6	7	7+	
D. K.	2 m			830	750		720		490	680			H.L.O. 2 cc.	Convalescent sepsis. Perc. oil ½ cc. during prelim. per.
T. B.	2 m	40	600	580	500		610			460			H. L. O. 4 cc.	Pylorospasm.
P. H.	2 m	22	540			420		430		410			H.L.O. 2 cc.	Prematurity.
S. U.	3 m	13	570	450		580	650	420		370			H.L.O. 2 cc.	Malnutrition. No diarrhea.
D. H.	3 m	0	350	410	580	850	1020			1200			H.L.O. 2 cc.	Malnutrition. Bitot spots.
H. T.	4 m	27		280	380	350			480				H.L.O. 4 cc.	Congenital glaucoma.
J. M.	4 m	13		500		560	630	560			530		H.L.O. 2 cc.	Convalescent meningitis.
E. Y.	6 m	20		600	780	500		550					H.L.O. 2 cc.	A.N.D.
G. A.	6 m	16		460	500	680		640					H.L.O. 2 cc.	A.N.D.
H. C.	7 m			420		640		590					H.L.O. 2 cc.	A.N.D.
J. R.	7 m	6	800	420	820		680						P.O. 2 cc.	A.N.D.
J. T.	7 m	20		730	840	700		650	650					Sarcoma.
L. H.	7 m		700	550	750		680		500				P.O. 2 cc.	Hydrocephalus. Perc. oil ½ cc. during perlim. per.
H. T.	8 m		680			1000		740					H.L.O. 2 cc.	A.N.D.
M. M.	8 m			790		1000	600		720		630		H.L.O. 2 cc.	Convalescent meningitis.
C. F.	9 m	6	810	740		1050	940	800		1060		1140	H.L.O. 2 cc.	Anemia, malnutrition. Serum protein 5.2.
D. G.	10 m	25		560		850	890		1060				H.L.O. 2 cc.	Subdural hematoma. Malnutrition.
F. J.	11 m	6		520	800		1090		1330	1200	1220	1260	H.L.O. 2 cc.	Anemia, thiamin deficiency. Malnutrition ser. prot. 5.6.

J. E.	12 m	10	520	570		640		540			560		Malnutrition. S.P. 5.3.
F. S.	13 m	20		260		360	480		800	560	640	700	P.O. ½ cc.	Atypical pneumonia.
W. S.	13 m	22		860	1090	770		720						
E. H.	12 m			510		1000		750						Chronic nutritional disturbance.
V. C.	13 m	27	410	530	830	760		650					H.L.O. 2 cc.	Malnutrition.
W. H.	16 m			550		590	860		850	750			H.L.O. 2 cc.	Convalescent from A.N.D.
J. D.	17 m	22	450	540	650		650						H.L.O. 2 cc.	Anemia.
A. W.	18 m	16	720	640		740		680						Convalescent. Typhoid fever.
C. M.	18 m	6	800	850		1100	950		1210	1060	910	770	H.L.O. 2 cc.	Anemia—malnutrition prolonged diarrhea.
G. B.	18 m			530	680		910						H.L.O. 2 cc.	Convalescent from operation—hernia.
L. W.	19 m	23		650		760	630							Anemia.
R. A.	23 m	27		620		820	1220			840			H.L.O. 2 cc.	Convalescent from operation—cleft palate.

Note: The significance of the initial vitamin A levels may be judged as follows:—Figures below ten are definitely associated with deficiency. They are also found in severe infection, in liver disease and often in chronic gastrointestinal disease especially celiac disease and pancreatic steatorrhea. Figures from 10 to 20 micrograms are definitely below normal. However, they occur in so many conditions in which deficiency is not a factor that they have little significance in diagnosing deficiency. Figures above twenty may be accepted as within normal limits.

Abbreviations: P.O. Percomorph oil; H.L.O., Halibut liver oil; A.N.D., Acute nutritional disturbance (diarrhea and vomiting); S.P., Serum protein.

case reaching 1,000 mgs. per cent. In one case with extreme malnutrition and subdural hematoma the lipids rose to 1,000 mgs. per cent shortly before death. No evidence of vitamin A deficiency was found at autopsy and as may be seen in the table the initial serum vitamin A was not at the deficiency level.

There were six cases recovering from an *acute gastro-intestinal disturbance* (diarrhea and vomiting). In all of them the lipids rose to some extent at least, and in three to definitely abnormal levels. The rise however was only temporary.

There was one case of *scurvy* with a rather low initial vitamin A level. This case showed no significant lipid reaction to vitamin A administration. In three cases there was a well marked but temporary lipid rise when tested during the period *following operation* in which general anesthesia was given.

DISCUSSION

From experimental work, it is evident that vitamin A is an important factor in lipid metabolism. (1). In vitamin A deficiency in rats, the serum lipid levels were found to be reduced.[2] (2). When vitamin A was given to normal rats in high dosage a temporary rise in lipid levels occurred. The phenomenon has also been found in other animals and in man. (3). When rats previously rendered deficient were given vitamin A in high dosage the rise in serum lipids was much greater and more prolonged.[2] This was interpreted as an example of increased sensitivity to a substance brought about by deficiency of the substance.

In the present work four of the babies showed a rise in lipids far greater than the average and much more prolonged. In only one of these was there definite evidence of vitamin A deficiency (Bitot spots in D. H.). In all, however, the serum vitamin A was absent or extremely low on the first examination, in the absence of severe infection and disease of the liver, conditions known to be associated with the low serum vitamin A levels. Moreover, in all four babies, the nutritional state was bad and other deficiencies were present. It is therefore not unlikely that at least some degree of vitamin A deficiency was present in all.

Sensitivity of the lipid response to vitamin A administration was recently shown to occur in convalescence from pneumonia in infancy with considerable regularity,[3] although the response was not as great

or as prolonged as in the deficient cases reported here, except in two instances in which there was reason to suspect deficiency. It must however be recalled that in older children a serum lipid rise occurred after pneumonia without vitamin A administration. This is mentioned to emphasize the fact that sensitivity of lipid response may occur under other conditions than possible deficiency. Moreover in the work reported in the present paper, there were a number of cases in which serum lipid sensitivity was present with no evidence of deficiency. In only one instance, however, was the lipid rise comparable with that in the deficient cases, a child with subdural hematoma who had become extremely malnourished.

The results reported here therefore suggest that, as in rats, a deficiency of vitamin A causes an increased sensitivity of the serum lipid response to vitamin A administration. Until we know more concerning the conditions governing serum lipid sensitivity, this phenomenon can be considered only as suggestive evidence of deficiency, not as a test by which deficiency can be determined.

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